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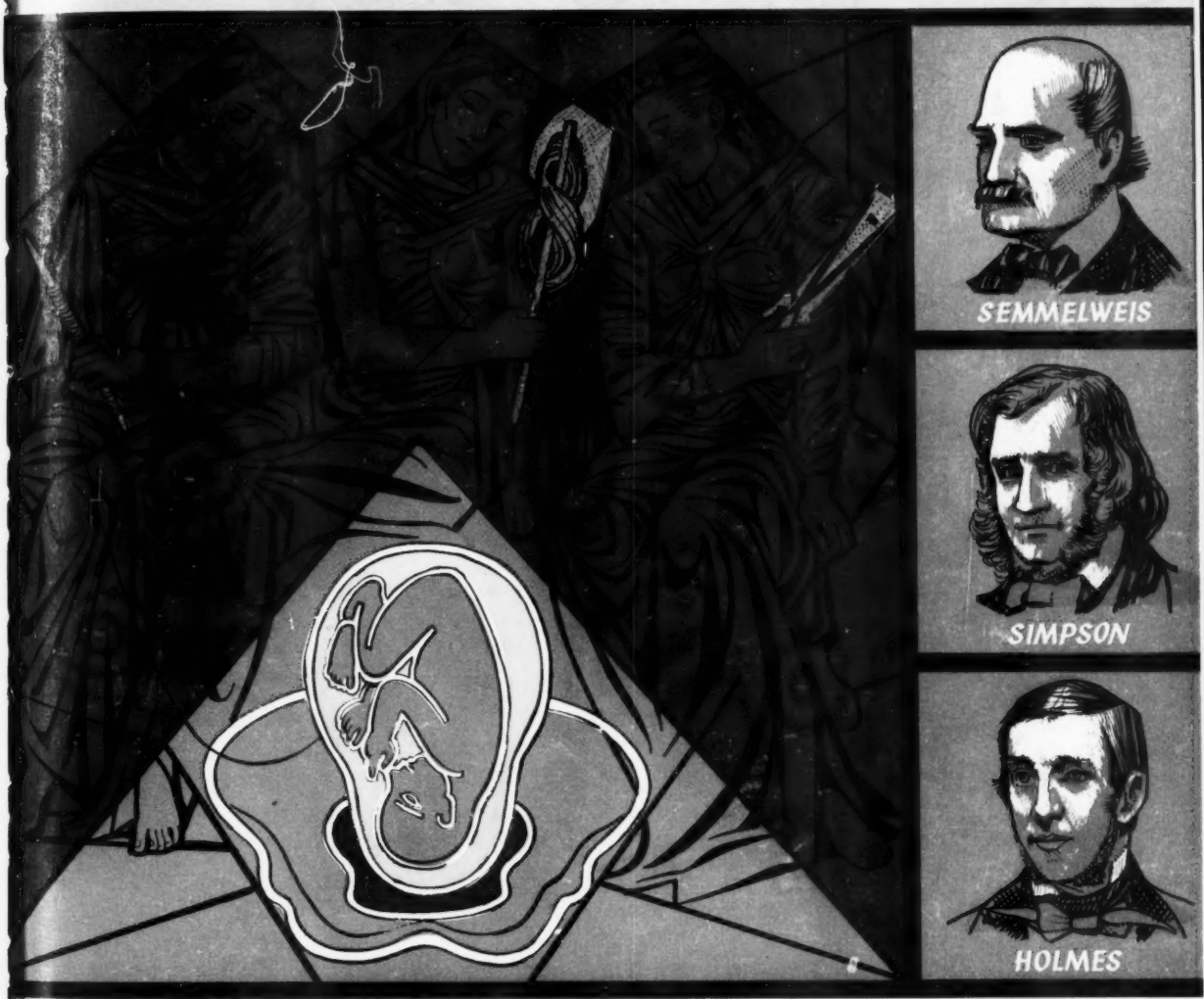

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FOR THE CONTINUING EDUCATION OF THE PRACTICING PHYSICIAN

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Diagnostic Clinic

The Clinical Use of Histamine

BAYARD T. HORTON*

MAYO CLINIC, ROCHESTER

THE subject I wish to discuss, namely, the clinical use of histamine (beta-iminazolyl-ethyl-amine) is an intriguing one and covers an extensive clinical field. A decade ago when Dr. Charles Best made a hurried trip to the Mayo Clinic to observe some of the early work that was being done on this substance, he remarked, "I would like to spend the rest of my life studying histamine." Several years later, Sir Alexander Fleming, after observing some of the work being done, remarked, "Histamine may prove more useful than penicillin."

In the time allotted for this diagnostic clinic, it is impossible for me to do more than touch upon the highlights of this subject and describe the use of histamine in the management of many seemingly unrelated clinical entities. Since many of the observations to which I shall refer represent work still in progress, the complete story cannot be told or written at this time. Statistical studies are being made, and the results of these studies will be reported at a later date.

Histamine has been known to the scientific world since 1907, when it was first prepared as a purely synthetic product by Windaus and Vogt.[1] In 1910, it was isolated from ergot by Barger and Dale.[2] Finally, in 1927, Best, Dale, Dudley and Thorpe[3] demonstrated its presence in living tissue. The first comprehensive study regarding the physiologic action of histamine in the experimental animal was carried out by Dale and Laidlaw[4] in 1910. Not a great deal of knowledge of this substance has been added since that time. Four years earlier, von Pirquet[5] had called attention to the close relationship between anaphylaxis and allergy, and it is interesting to note that Dale and Laidlaw concluded their report by saying, "We content ourselves with recording, as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to a large extent those of poisoning by beta-iminazolyl-ethylamine" (histamine). Much evidence which is now available strongly suggests that the mechanism involved in anaphylaxis and allergy is a manifestation of the same phenomenon.

From year to year, bits of information have been added to the results of their basic studies, but the story is still not complete. No attempt is being made in this report to review the literature on histamine. Anyone interested in the literature on this subject will do well to read Selle's[6] recent comprehensive review. The literature on this subject is confusing because it has often been assumed that the physiologic effects which have been observed in experimental animals also apply to human beings, but such is not always the case.

In order to understand the clinical use of histamine, it is necessary to appreciate its physiologic effects in man. It is a substance that can be isolated from practically every human tissue except that of the central nervous system. It is found in peripheral sensory nerves but not in peripheral motor nerves.[7] The significance of these facts must await the results of future studies. Histamine is a normal constituent of human blood and is found chiefly in the granular leukocytes.[8-10] The exact manner in which histamine is held in the granular leukocytes of

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the blood and in the fixed cells of the body is not known, but the rapidity with which it can be liberated strongly suggests that it is not bound permanently to the cellular protoplasm. The presence of this agent in the granular leukocytes and in the fixed cells does not give rise to clinical signs and symptoms until released in its free form.

The concentration of histamine in the human blood is reported to be approximately 4 micrograms per 100 cc. The range in a normal person is perhaps 2 to 7.5 micrograms per 100 cc. of blood. Although the concentration of histamine remains constant in the blood of normal persons, it tends to fluctuate to a marked extent in persons who have allergic diseases. There is no simple, accurate chemical method for determining the concentration of histamine in the blood, although one is greatly needed. Code's[11] modification of the original method of Barsoum and Gaddum[12] has been used by the majority of recent investigators for determining the amount of histamine in various tissues.

BAYARD T. HORTON

It has long been my opinion that the common denominator of allergic diseases and of some diseases not now recognized as being allergic in nature is an underlying localized vasodilatation, altered capillary permeability and resulting edema provoked by the local release of histamine or histamine-like substances. In the skin, localized edema manifests itself clinically as urticaria and angioneurotic edema; in the nasal mucosa, as nonseasonal vasomotor rhinitis and, at certain seasons of the year, as hay fever; in the labyrinth, as Ménière's disease and, in the optic nerve, as retrobulbar neuritis. Many spinal and cerebral diseases of sudden onset can be adequately explained only on an allergic basis. Ferraro[13] said, "The pathologic syndrome of demyelinating diseases appears plausible as the expression of an allergic reaction of the nerve tissue." Although the fundamental pathologic processes involved in the production of localized edema are the same, the resulting signs and symptoms depend upon the site of the edema. It is my impression that the abnormal release of histamine from sensitized cells and tissues probably gives rise to more of these signs and symptoms than the medical world has yet realized. With this conception of a common cause applied to many seemingly unrelated clinical problems, I have used histamine as a therapeutic agent with marked success in many cases.

Dragstedt[14] said, "The fundamental effects of histamine are: a contraction of smooth muscle, a dilatation and increased permeability of capillaries and an increased secretion of various glands." Code[15] made a similar statement and added a note regarding histamine as the chemical mediator for cutaneous pain.

PHARMACOLOGIC ACTION OF HISTAMINE

In order to rationalize the therapeutic use of histamine in such a wide variety of clinical problems as I have encountered at the Mayo Clinic during the past decade, it is necessary to focus attention on some known actions of histamine in man.

Effect of histamine on the circulatory system—Histamine dilates the arterioles, venules and capillaries in man.[16] It is doubtful that it ever constricts smooth muscle in normal human beings. The action of the drug on the arterioles is variable in different animal species. For example, in rodents, histamine produces marked arteriolar constriction; in the cat, it produces slight arteriolar constriction, whereas, in the dog, monkey and man it produces arteriolar dilatation.[17] The intravenous administration of this drug produces cutaneous vasodilatation which appears first over the face and neck, and, if the rate of administration is rapid, it produces cutaneous vasodilatation which gradually extends downward over the upper extremities and thorax, reaching the lower extremities only toward the end of the period of observation. The cutaneous vasodilatation varies with the rate of administration of histamine. It is more marked in redheaded persons and blondes than it is in brunettes. This drug causes a definite increase in skin temperature and heart rate and a slight decrease in diastolic blood pressure (Figure 1). The blood flow in the 4 extremities gradually increases in proportion to the dose used. The average increase in blood flow

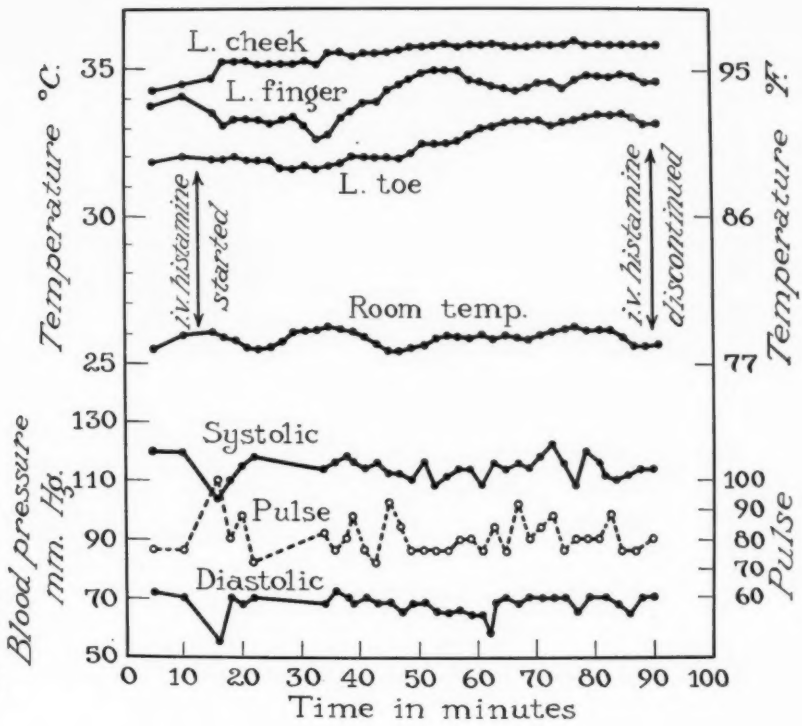

FIGURE 1. Effects of intravenous administration of histamine, under basal conditions, on the skin temperature, pulse and blood pressure.

over the control values which I have observed was 244 per cent in the left arm, 120 per cent in the right arm, 76 per cent in the left leg and 28 per cent in the right leg. The changes in skin temperature, heart rate, blood flow and blood pressure gradually subsided and the values returned to the control level shortly after the infusion had been stopped.[18]

The results of a recent study indicate that histamine causes a greater increase in blood flow to the central nervous system than any other drug known (Figure 2). Photographic records of the pulsations of the human brain indicated that the subcutaneous administration of 0.25 mg. of histamine base produced a 725 per cent increase in the amplitude of the pulsations of the brain, whereas the intravenous administration of an 0.0011 per cent solution of histamine diphosphate at rates ranging from 18 to 30 drops per minute caused a 300 per cent increase in the amplitude of the pulsations of the brain.[19] In a comparative study, the intravenous administration of 50 mg. of nicotinic acid produced only a 65 per cent increase in the amplitude of the pulsations of the brain even though it caused the face to become bright red in color.

At the clinic, we have had the opportunity of observing visually the effect of intravenous administration of histamine on the cerebral cortex in a case in which exploratory craniotomy was performed with the aid of local anesthesia. Within 30 seconds after the intravenous injection of the drug was begun, the cortex became fiery red and vessels which usually were hardly visible became prominent. The drug also causes an increase in the pressure of the cerebrospinal fluid.

Anrep[20] has reported that histamine produces dilatation of the coronary arteries in the human heart-lung preparation. Presumably, this occurs in living persons. Essex and his co-workers[21] have reported that histamine increases the rate of coronary blood flow in the experimental animal. The drug has no decided direct cardiac action, but the heart rate and cardiac output are increased as a reflex response to vasodilatation.

Effect of histamine on capillary permeability—Intra-arterial injection of minute amounts of histamine produces a sudden and dramatic increase in capillary permeability with resulting edema in the tissue supplied by the artery in question.[22,23] When the drug is administered clinically according to the method which will be described, it apparently does not cause any alteration in capillary permeability.

Local effects of histamine—An intradermal injection of histamine produces dilatation of those

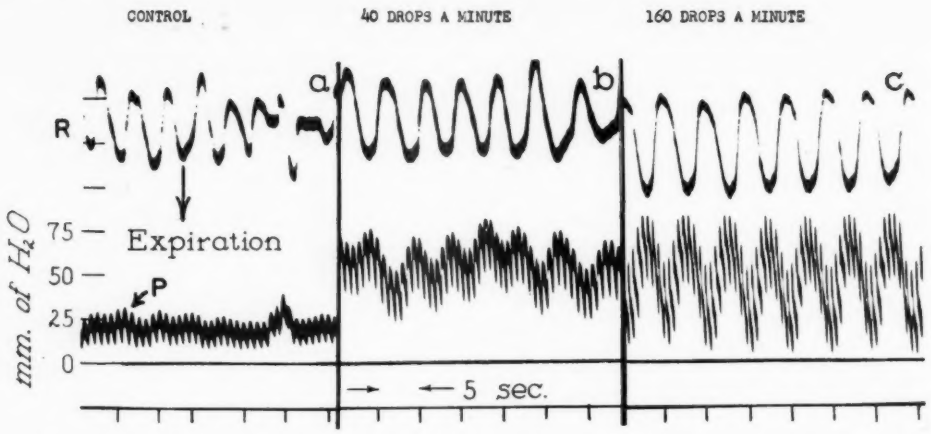

FIGURE 2. Effects of intravenous administration of histamine (1:250,000 dilution) on the amplitude of pulsations of the human brain. R—respiration; a—control period; b—five minutes after starting intravenous injection of histamine. The graph indicates an increase in intracranial pressure as well as an increase in the amplitude of pulsations. c—55 minutes after injection of histamine was started. An increase in the amplitude of pulsations is even more evident at a more rapid rate of administration.

capillaries in direct contact with the drug, a diffuse flare due to dilatation of surrounding arterioles resulting from local axon reflexes, and an area of edema. This reaction is similar to Lewis' triple response mechanism. There is no convincing evidence that intracutaneous injection of histamine can be used to determine whether a patient is "histamine sensitive" or "histamine insensitive."

Effects of histamine on oxygen consumption and basal metabolism—The administration of histamine causes an increase in oxygen consumption. So far as I have been able to determine, this increase is roughly proportional to the rate at which the drug is administered. It ceases soon after the administration of the drug has been stopped, thus differing from the increase caused by such "calorigenic" substances as thyroxin. The maximal increase which I have observed in the basal metabolic rate was from a level of −14 per cent to +96 per cent. During the intravenous administration of histamine there is an increase in the oxygen content of the venous blood.[24] In 1 case in which an 0.0011 per cent solution of histamine diphosphate was administered intravenously at the rate of 160 drops per minute, the oxygen saturation of the venous blood, which initially was 60 per cent, increased to 94.3 per cent, an actual increase of 34.3 per cent. In other words, the venous blood assumes an arterial character as a result of the rapid intravenous administration of the drug. This dramatic change can be demonstrated by even a casual observer if he compares samples of venous blood obtained before and during the intravenous administration of histamine. In order to be valid, these observations must be carried out under conditions used in performing a basal metabolic test.

Histamine as a secretagogue—Histamine has been known to increase gastric acidity since 1920 when Popielski[25] administered the drug subcutaneously to dogs with gastric fistulas. Carnot, Koskowski and Libert[26] in 1922 were the first to study the secretion of gastric juice in man after histamine had been administered subcutaneously. In 1927, Mogena[27] reported that the intravenous administration of histamine did not have any influence on gastric secretion. Best and McHenry,[28] in a comprehensive review on histamine in 1931, commented on this report as follows: "A slow intravenous injection would undoubtedly give positive results in man."

In 1940 Peters and I[29] demonstrated that the resulting increase in gastric acidity in man is approximately the same at different rates of administration of histamine. The rise was greater in men than it was in women, and greater in young persons than in older ones. The gastric secretion affords a very delicate measure of the action of histamine in man. The gastric cells were observed to react to the intravenous administration of histamine over prolonged periods.

Wolf and Wolff[30] reported their observations on a male patient with a permanent gastric fistula. When histamine was administered to this patient, direct observation of the gastric mucosa showed an increase in blood flow and in gastric motility and acidity.

Effects of histamine on the electrocardiogram—Peters and I[31] have observed certain significant

changes in the electrocardiograms in 24 of 25 cases studied. The most common change was loss of amplitude of the T waves in different leads, sometimes in all leads, which, in some cases, proceeded to either the isoelectric level or to inversion of the wave. The first effect appeared most frequently in lead III, next in lead II, then in lead CR_2 and lead I, and finally in lead IV-R. The effect of histamine on the T waves disappeared within five to 15 minutes after injection of the drug was discontinued. The cardiac rate was increased on an average of 26 beats per minute. Impairment in atrioventricular conduction was observed in only 1 case, and this continued for only a short time. Premature ventricular contractions were observed after the administration of histamine in 4 cases, and left axis deviation was observed in 6 of the 25 cases.

Electrocardiographically, the effects of administering histamine intravenously to human beings in the manner which will be described may be considered of minor physiologic importance. No clinical evidence of permanent cardiac damage has been observed.

Effects of histamine on the glands of internal secretion—In the experimental animal, histamine metabolism seems to be under the influence of certain endocrine glands. Rose and Browne,[32] as well as Marshall,[33] have observed an increase in the histamine content of the skin and tissues of the rat after adrenalectomy. Gotzl and Dragstedt[34] report a decrease in the histamine content of the skin and tissues of the rat after thyroidectomy.

I CAN only postulate regarding the action of histamine on the glands of internal secretion in man. It is well established that histamine causes the liberation of epinephrine from the medullary portion of the human suprarenal gland. This can be demonstrated in cases of a pheochromocytoma,[35,36] and can be used as a test for this obscure tumor. A dramatic rise in blood pressure results, owing to an outpouring of epinephrine. This represents a paradoxical reaction to histamine. The action of histamine on the cortex of the suprarenal gland probably can be measured indirectly by the response of the eosinophils in the blood, as proposed by Thorn and associates.[37] Eosinophilic response is reputed to be the most sensitive indicator of release of steroids from a functioning suprarenal cortex. In the dog, the intravenous administration of histamine produces a dramatic decrease of approximately 80 per cent in the eosinophil count in a period of 10 to 15 minutes whereas ACTH and epinephrine produce a decrease of approximately 60 per cent in four hours.[38] When an 0.0011 per cent solution of histamine diphosphate was administered intravenously at 200 drops per minute to a man, Kiely, Bain, Mathieson and I[39] observed a 41 per cent drop in the eosinophil count in 40 minutes whereas, in the same case, a 61 per cent drop in the eosinophil count in four hours followed the administration of 25 mg. of ACTH.

A total of 11 patients with multiple sclerosis were tested in this same manner, and there was a prompt drop of the eosinophil count in the peripheral blood in all 11 patients. The drop ranged from 18 to 91 per cent in 20 minutes. The maximal drop in the eosinophil count at the end of 40 minutes was 62 per cent.

It would seem as if the cortical discharge of steroids in man occurs more promptly following the administration of histamine than it does after the administration of any other agent thus far tested.

Many of the phenomena observed after the clinical use of compound E (cortisone) and ACTH have been observed after the clinical use of histamine. An increased sense of well-being with a tendency toward euphoria, an increase in appetite, a feeling of warmth, especially in the extremities, and an increase in muscular strength have been observed during the years that I have used histamine therapeutically.

My experience with the use of histamine as a therapeutic agent dates from 1927. Since that time, my interest in this drug has been increased materially with the revelation that the drug would completely and often permanently eradicate the symptoms of innumerable conditions in which it never had been tried, as well as many diseases in which the use of other medication has proved fruitless. I have treated acute multiple sclerosis[40] and other demyelinating diseases of the central nervous system, Ménière's disease and associated deafness,[41-46] histaminic cephalgia[47,48] and other types of headache and facial pain,[49-52] many interesting ophthalmologic conditions such as retrobulbar neuritis,[53] as well as other bizarre types of pain which will be reported in detail at a later date. Perhaps I should parenthetically add the following thought: It seems to me as if the successful treatment of many of these conditions was largely attributable to the fact that I did not know when to stop histamine therapy.

CLINICAL ADMINISTRATION

Intravenous administration—My procedure varies only in the concentration of the solution used and the rate at which it is administered. To prepare a standard solution I add 2.75 mg. of histamine diphosphate to 250 cc. of isotonic solution of sodium chloride. The resulting solution contains approximately 0.0011 per cent of histamine diphosphate and each cubic centimeter of the solution contains approximately 0.004 mg. of histamine base. This is

the standard solution which I administer intravenously in the treatment of Ménière's disease and associated deafness, multiple sclerosis, retrobulbar neuritis, chorioretinitis, corneal ulcer and hemiplegia.

In cases of migraine and tension headache, I frequently use a more dilute solution, which is prepared in the following manner. One cubic centimeter of 2.75 per cent solution of histamine diphosphate is added to 500 cc. of isotonic solution of sodium chloride. The resulting solution contains approximately 0.00055 per cent of histamine diphosphate and each cubic centimeter of the solution contains approximately 0.002 mg. of histamine base. This solution is often used in cases in which the patients are more sensitive to histamine. In a few cases, I have found that it is necessary to use a 0.000055 per cent solution of histamine diphosphate.

When histamine is administered intravenously, I begin the injection at a very slow rate and attempt to increase it gradually during the first and subsequent treatments. An effort is made to obtain the maximal vasodilation; however, the rate is always kept below a level that will cause any discomfort to the patient. The maximal amount for one treatment is 250 cc. of the 0.0011 per cent solution of histamine diphosphate. Although many patients tolerate administration at the rate of only 32 drops per minute and a few tolerate administration at only a fourth that rate, others may tolerate the administration of 60 to 80 drops per minute. In order to avoid weakness and fatigue on the part of the patient, I have limited the length of time for the administration to one and a half hours daily or every other day with only an occasional exception.

One should emphasize the importance of having food in the patient's stomach at the time the histamine is administered, so that the excess of gastric acids may be absorbed. If gastric distress is noted during the administration of the drug, a colloidal suspension of aluminum hydroxide, such as amphojel, should be administered prior to each injection. In only one instance has a gastric ulcer occurred,[34] although I have given over 90,000 intravenous injections of histamine. The patient had reported for his treatment without eating, and this was not discovered until two weeks had elapsed and an ulcer had developed.

I do not think of this procedure as a "rapid desensitization," but rather in terms of the degree and extent of the vasodilatation that are produced. I never have observed any reaction from the administration of histamine but some physicians have reported that the administration of the drug does produce a reaction. The reactions which have been observed by these physicians have not been due to the histamine itself but rather to the presence of pyrogenic substances in the tubing or other equipment used in administering the drug. A few pharmaceutical houses recently have placed on the market a disposable rubber tubing which should be used when histamine is administered. If this tubing is used, reactions can be avoided. In 1 case which I have observed, the drug has been administered for more than five and a half years without producing any reaction. In this period, more than 619 injections of the drug have been administered.

Subcutaneous administration—My procedure for the subcutaneous administration of histamine is as follows:

I use the contents of a 1 cc. ampule of 0.275 mg. of histamine diphosphate per cubic centimeter, which contains 0.1 mg. of histamine base. Of this ampule, I use 0.05 cc. for the first dose, which is administered subcutaneously. Two injections are administered daily about six to eight hours apart. Each injection is increased by 0.05 cc. until 0.50 cc. is given. In some instances, this amount is not adequate and it is necessary to continue to increase the amount until 0.75 cc. or even 1.0 cc. is reached. Adequate dosage is determined by the patient's response. If no immediate flushing of the face or throbbing is experienced with the injection and if the patient's symptoms decrease in severity or frequency, the procedure is adequate. However, if the symptoms are aggravated or seem to be precipitated by the injections, the patient may be undergoing "sensitization" rather than "desensitization." In such a case, the subsequent dose is reduced by a half, and again the amount administered at each injection is increased by increments of 0.05 cc. to a level just below that amount which precipitated the symptoms. This amount is then injected twice daily as the maintenance dose. The patient is instructed in the technic of administering the injections himself (whether the dose is 0.25 cc. or 0.75 cc.) and is told to continue them twice daily at home for two or three weeks and once daily thereafter for an indefinite time. Some patients find it necessary to continue to use 1 or even 2 or 3 injections daily at home in order to remain free of symptoms. There is no harm in continuing with maintenance doses of histamine for a lifetime if necessary. I am convinced that the use of smaller amounts of histamine at more frequent intervals controls symptoms more satisfactorily than larger amounts administered subcutaneously only once daily or every other day.

After a long period of freedom from symptoms, many patients are lulled into a false sense of security, and discontinue the injections of maintenance doses. Many others report a recurrence of symptoms coincidental with an infection of the upper part of the respiratory tract. The maintenance dose

then is inadequate, and resuming the desensitization schedule is often difficult because of the change in the patient's sensitivity. When experiencing a recurrence of headaches, many patients with histaminic cephalgia report attempting to resume the desensitization schedule and increasing the dose to the former maintenance level without realization that, with a recurrence of the attacks, the sensitivity to histamine is greater than it was during the previous episode. The reason for this has not been determined. Only careful reports and observations of the patient's symptoms and response to injections in each 24 hours will give a clue to the schedule most satisfactory for each patient; hence, my expression that each schedule has to be "tailor-made" to fit the individual patient.

When a patient reports for readjustment of his schedule it frequently is necessary to administer Kendall's whole cortical extract before administering the first injection of histamine (0.05 cc.). I repeat the intravenous injections of whole cortical extract and usually administer 3 cc., 4 cc. and 5 cc., respectively, at hourly intervals until a total of 3 or 4 such injections has been given. Occasionally a total of 50 cc. of the whole cortical extract is administered. Recently, I have substituted cortisone for the whole cortical extract. I administer 100 mg. of cortisone intramuscularly daily for three or four days, or longer, before resuming the subcutaneous injections of histamine. For some strange reason, the whole cortical extract, as well as cortisone, seems to reduce the patient's sensitivity to histamine. In some cases, this does not adequately reduce the sensitivity, and a more dilute solution of histamine must be used. This represents the exception. In such cases, a special solution half the usual strength is prepared. However, the same schedule is followed by increasing the injections by 0.05 cc. increments each time until a satisfactory maintenance dose is reached. I have not had sufficient experience with the use of cortisone to make a final statement regarding the amount necessary to administer to alter the patient's sensitivity to histamine. My experience thus far has been limited to the treatment of patients with histaminic cephalgia.

REPORT OF CASES

Case 1. Cold allergy associated with systemic histamine-like reaction simulating anaphylactic shock in an experimental animal—A girl, 14 years of age, who was strong and healthy, had gone swimming on July 4, 1941. About two minutes after entering the water, she had become dizzy, had fainted and had to be rescued. The skin of the whole body had become scarlet and edematous. Even the girl's parents had not recognized her when she had been rescued from the water. The pulse rate had been more than 200 beats per minute, and breathing had been difficult. The patient had been revived by artificial respiration, but the edema had persisted for about 42 hours. Strange as it may seem, she had been swimming in the same pool on May 30, 1941, at which time the water had been definitely colder than at the time she collapsed. She had experienced no ill effects while swimming on May 30.

She was still hypersensitive to cold when she was observed at the clinic in 1941. As a special test, a tourniquet was placed around her right arm so as to occlude the circulation, and her right hand was immersed in water at 10° C. for seven minutes. When her hand was removed from the water, it was cold, but not swollen. There was no swelling or reaction until the tourniquet was released. She then went into a mild shocklike state accompanied by a drop in blood pressure and rise in pulse rate. The swelling of the right hand became so marked that she was unable to close it, and residual swelling continued for more than 16 hours.

The value for the blood histamine, which was determined by the method of Code immediately before the hand was immersed in the water, was 0.029 gamma per cubic centimeter. The value after the hand was removed from the water and immediately after release of the tourniquet was 0.04 gamma per cubic centimeter.

A course of histamine desensitization was carried out according to my standard method for two weeks. At the time of the patient's dismissal, she was advised to continue the injections twice daily at home, and to increase the dose gradually to about 0.5 cc. if she could do so without any reaction. She also was told to immerse her hands in water at 10° C. for one minute twice daily, and gradually to increase the period of immersion to seven minutes.

Comment on Case 1—This case reminds one of Richet's classic description of anaphylactic shock in his dog, Neptune, in 1902. He had given the dog 0.1 cc. of "a certain glycerine extract," but no ill effects were noted. When he repeated this same dose of the extract 22 days later the animal became extremely ill and died within 25 minutes. It has been demonstrated repeatedly in recent years that anaphylactic shock in such an animal is accompanied by a rise in the concentration of histamine in the blood. The similarity between the shocklike state observed in this patient and anaphylactic shock in the experimental animal seems comparable in every way.

It would seem that this patient was sensitized to cold when she went swimming on May 30. She remained perfectly well from that time until July 4, when she went swimming again in the same pool when the water was definitely warmer. Nevertheless, she collapsed and had to be rescued. The second exposure is equivalent to the shock dose in the previously sensitized experimental animal.

In studying this case, it was necessary to determine whether the shocklike state was of neurogenic or chemical origin. The special tourniquet test is extremely important, because it seems to eliminate definitely a reflex basis for the systemic

response. It suggests that a chemical substance was produced in the skin following exposure to cold and that an accumulation of this substance in the hand in sufficient concentration, when suddenly released into the general circulation, produced an exaggerated systemic reaction. In our original studies of cold allergy in 1927, Brown and I postulated that this hypothetical substance was histamine. This now seems definitely established.

Case 2. Arteriosclerosis of the central nervous system associated with severe dizziness, vertigo and depression—A woman, aged 77 years, had had a sudden attack of dizziness and vertigo June 9, 1945. There had not been any tendency toward spontaneous improvement, and she finally was brought to St. Marys Hospital in an ambulance on August 27, 1945, for emergency treatment. She was totally incapacitated and as one sat by her bedside and attempted to interview her, she kept her eyes closed and held on to the bed rails to keep from falling on the floor. The clinical picture seemed to be best explained on the basis of arteriosclerosis of the central nervous system. An otolaryngologist did not feel that the patient had ordinary Ménière's disease.

The results of routine physical examination and laboratory tests were essentially normal. Her physical condition seemed good for a woman of her age. Examination revealed complete loss of hearing in the left ear, which had been present since childhood. Her blood pressure was 154 mm. of mercury systolic and 84 mm. diastolic. She had not responded to the usual forms of therapy before she was brought to the clinic. The neurologists felt that her symptoms were due to arteriosclerosis of the central nervous system. She was profoundly depressed, primarily because of her husband's recent death.

Intravenous histamine therapy was instituted, and she received a total of 39 injections according to my standard method. Nearly all of her symptoms disappeared in 15 days and she was able to dance at the time of her dismissal. Her sons said that she looked and behaved like a new woman, and she was very cheerful.

Comment on Case 2—It was interesting to follow this patient's progress and recovery. The improvement can best be explained on the basis of the increase in blood flow to the central nervous system provoked by the daily use of intravenous histamine therapy. She said that she felt 20 years younger at the time of her dismissal.

HISTAMINE should prove useful in the future management of this type of clinical problem. Patients with arteriosclerosis of the central nervous system theoretically should be benefited by this type of therapy.

Case 3. Allergic arthritis and optic neuritis—A man, aged 46 years, first came to the clinic on September 11, 1940, because of partial loss of vision in the right eye of seven months' duration and intermittent swelling and pain in the arms, legs and shoulders of about a year's duration. On awakening on February 16, 1940, he had noted a dark spot in front of the right eye which had persisted without any tendency toward spontaneous improvement. Certain joints had become red, swollen and painful. Approximately a year before he came to the clinic, he had noted redness and swelling of the dorsum of the left foot and the tips of the fourth and fifth toes. The swelling and redness had seemed to shift from joint to joint without leaving any definite residua. The family physician had suspected that the patient had gout.

Ophthalmoscopic examination of the right eye revealed structural fullness of the disk with blurring of the margins, pallor, grade 2, and some colloid deposits in the substance of the disk. The veins were slightly full with minimal narrowing and sclerosis of the retinal arteries. Examination of the perimetric field of the right eye revealed a very dense paracentral scotoma and the ophthalmologist felt the defect was characteristic of optic neuritis. The visual acuity was 6/60. Ophthalmoscopic examination of the left eye revealed a structurally full disk of good color, with the retinal veins engorged and dark. The left perimetric field was essentially normal and the visual acuity was 6/6.

The results of general physical examination and routine laboratory tests were normal except for swelling and pain at the base of the fourth and fifth fingers of the right hand exaggerated by exercise which interfered with his work. It was necessary for him to use sedatives at night in order to sleep. When not using the hand, he was conscious of slight pain in the interspaces between the heads of the fourth and fifth metacarpal bones. The value for the uric acid was 2.9 mg. per 100 cc. of serum.

Histamine was administered intravenously on two successive days to determine whether it would prove of any help from the standpoint of the arthritic pain. I was concerned only with the problem of allergic arthritis and had relief of the arthritic pain in mind when treatment was instituted. It was assumed that the visual defect in the right eye was permanent and not amenable to treatment. Six tenths of a milligram of histamine base in 150 cc. of isotonic solution of sodium chloride was administered intravenously at the rate of 80 drops per minute, in an environmental temperature of 78° F. and in a humidity of 40 per cent. The second injection was given within 24 hours in the same manner, except that the rate was 44 drops per minute. He obtained complete relief of pain and swelling in the hand and, what is even more interesting, marked improvement occurred in the vision in the right eye. Subjectively, he felt as if his vision had returned to normal. The ophthalmologist who rechecked the perimetric field of the right eye reported, "There is a definite improvement in the visual field of the right eye." The vision had improved to 6/15. The patient apparently was not aware of the improvement of vision until after the second injection had been administered, when he spontaneously remarked, "I can see much better out of my right eye." He could see the second hand on his watch, which he could not do previously. He also said, "I can see the whole watch when looking at it with my right eye." Before

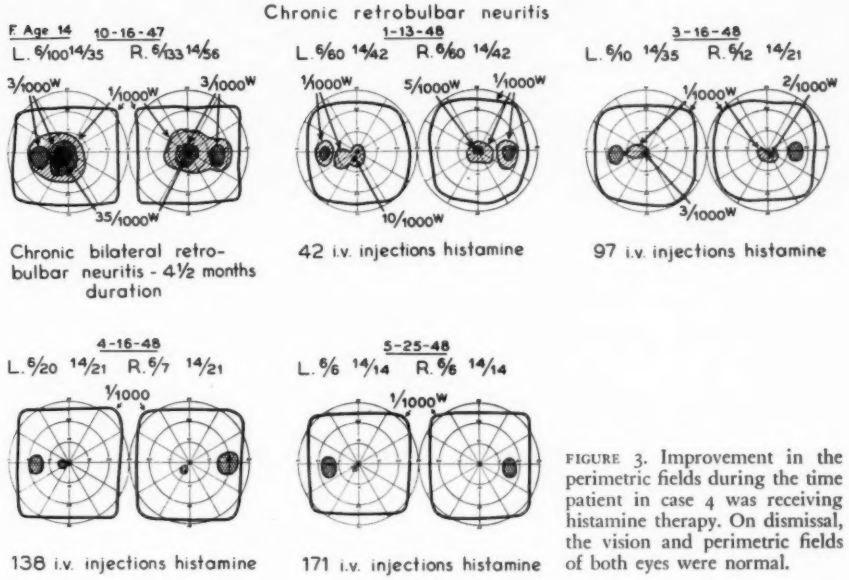

FIGURE 3. Improvement in the perimetric fields during the time patient in case 4 was receiving histamine therapy. On dismissal, the vision and perimetric fields of both eyes were normal.

treatment was instituted, he could see only a part of the watch.

At the time of his dismissal, he was taught to inject the histamine subcutaneously and was advised to continue the injections every other day after he returned home. When he was observed at the clinic one year later, his vision was still 6/15 in the right eye. He had not had any recurrence of the arthritic symptoms. Although he returned to the clinic in 1942, 1943 and 1944, examination disclosed that his vision had remained good, and he said that he had not had any recurrence of arthritis in the respective intervals.

Comment on Case 3—In this case, it seems reasonable to assume that edema was the underlying etiologic factor in the production of two seemingly unrelated clinical entities, namely, allergic arthritis and retrobulbar (optic) neuritis. The dramatic manner in which both of these conditions improved after the intravenous injection of only 2 doses of histamine seems to indicate the validity of this assumption.

Ccse 4. Bilateral retrobulbar neuritis—A girl, 14 years of age, was brought to the clinic on October 15, 1947, because of progressive loss of vision in both eyes of about four and a half months' duration. Early in June of that year, she had first noted that she was unable to see writing on the school blackboard, and, when she had returned to school the following September, she still had been unable to see any better. Immediately thereafter, she had been taken to a university hospital where a neurologist and an ophthalmologist had told her father they did not believe that any treatment would be of help.

When the patient was examined at the clinic, vision was 6/133 in the right eye and 6/100 in the left eye (metric system) (Figure 3). A slight pallor of the temporal portion of each optic disk was noted. Examination of the visual fields disclosed central scotomas with very dense nuclei. The results of general examination, neurologic examination and special tests were normal.

Over a period of approximately seven and a half months she received a total of 183 intravenous injections of histamine according to my standard method (once daily except on Sundays and holidays). On frequent occasions, her perimetric fields were rechecked, and on each occasion the examination revealed improvement in each eye. Her progress was slow. She seemed to gain weight, and her general feeling of well-being improved. A natural reserve, which had been noted when she first came to the clinic, soon gave way to a more friendly, voluble personality.

At the time of her final examination on June 7, 1948, the visual acuity of each eye had improved to 6/6. She was able to read almost the finest print on the test cards without any difficulty. The slight pallor remained in the temporal portion of each optic disk. When she again returned a year later (June, 1949), her vision and visual fields were normal. During the school year of 1948 and 1949, she led her class. In a letter written in the latter part of the summer of 1949, she said that her vision was entirely normal and that she was looking forward to returning to school.

Comment on Case 4—In this case, symptoms of retrobulbar neuritis had been present for four and a half months before the administration of histamine was started, and no improvement had been noted during that time. One naturally wonders whether spontaneous recovery would have occur-

red if histamine had not been administered. My colleague, Dr. H. P. Wagener, senior consultant in the Section on Ophthalmology, has pointed out that spontaneous recovery will not be complete unless it begins within three weeks after the onset of retrobulbar neuritis.

In a few cases of retrobulbar neuritis in which the administration of typhoid vaccine had proved ineffective, Wagener and I obtained successful results by administering histamine intravenously. In 1 case in which a woman had had a scotoma for about six years, the visual acuity and the visual field returned to normal.

Compared with other forms of therapy, intravenous histamine therapy is more universally applicable, is less discommoding to the patient, does not require hospitalization, and results in a more complete recovery of vision, especially in cases of chronic retrobulbar neuritis.

Case 5. Pain of acute gout—A man, aged 54 years, came to the clinic on September 25, 1946, because of severe pain which was situated over the left eye and extended to the occipital region. Although I later saw him in consultation because of the pain in the head, I am reporting this case primarily because of the pain of acute gout and its prompt relief by the intravenous administration of histamine. The attacks of pain in the head had occurred for three years and had been precipitated by sneezing, coughing or changes in temperature. The history revealed that the patient had coronary heart disease but it did not disclose any indication of gout at that time. Cocainization of the left sphenopalatine ganglion relieved the pain in the course of an attack. Cauterization of the sphenopalatine ganglion with a 50 per cent solution of silver nitrate resulted in about 90 per cent freedom from pain. Examination of the ears, nose and throat revealed moderate atrophy of the mucous membrane and a patent window in the nasal septum which was the result of a previous operation. The diagnosis was coronary heart disease and sphenopalatine ganglion syndrome. The patient was dismissed on October 5, 1946.

The pain in the head recurred two weeks later, and the patient returned to the clinic on January 14, 1947. There was no essential change in the clinical picture, and the general and neurologic examinations did not disclose any significant abnormality. The left sphenopalatine ganglion was cauterized with 25 per cent trichloracetic acid but this treatment did not produce any relief.

I first saw the patient on January 21, 1947, because of the attacks of pain in the left side of the head which were still precipitated by sneezing or coughing. A dose of 0.3 mg. of histamine base was administered subcutaneously as a provocative test, but this did not reproduce the pain in the left side of the head. It did produce some substernal distress which was relieved by amyl nitrite. At that time, he was having as many as 10 to 12 attacks of pain in the head in 24 hours.

At 3:25 P.M. on January 23, 1947, I had occasion to see him again because of severe pain of acute gout. It was a question as to whether or not intravenous administration of histamine would influence the acute pain. The night before, he had been awake all night because of the pain and finally had to be admitted to St. Marys Hospital for emergency treatment. The pain and swelling of the involved joint had been present for 56 hours. He was brought to my laboratory in a wheel chair. With the use of crutches and without putting any weight on the right foot, he was able to hobble from the wheel chair to a cot. The pain was localized in the right metatarsophalangeal joint, which was red and swollen. The surface temperature of the involved joint was 91° F. whereas the surface temperature of the left metatarsophalangeal joint was 84° F.

I immediately administered an 0.0011 per cent solution of histamine diphosphate intravenously at the rate of 44 drops per minute. Within nine minutes after the injection of histamine was started, the pain in the right metatarsophalangeal area was markedly reduced in severity, and within 20 minutes he was entirely free of pain. There was a 25 per cent decrease in the redness and swelling around the joint. After the injection had been continued for an hour and a half, he was able to walk 18 feet from the cot to the wheel chair and could bear considerable weight on the right foot. Passive motion of the right great toe was possible without producing pain, but it had been impossible prior to therapy. The value for the uric acid was 7.6 mg. per 100 cc. of serum immediately before treatment was started, and immediately after treatment was discontinued it was 6.1 mg. per 100 cc. The patient did not have any recurrence of acute pain but there was still some redness around the right metatarsophalangeal joint on the following day although he could move the toe without pain. Intravenous administration of histamine diphosphate in the same manner on that day produced additional improvement in the appearance of the redness and swelling of the involved area. Furthermore, I could exert a fair amount of pressure over the joint without producing discomfort. An antigout regimen was instituted after the second intravenous injection of histamine.

Comment on Case 5—This case is of interest because of the marked relief of pain which occurred within nine minutes after the intravenous injection of histamine was started, and because of the complete relief obtained in 20 minutes. There can be no question about these observations and the relationship of histamine to the relief of pain of acute gout. The gout itself remained unchanged.

Incidentally, further questioning disclosed that this was the patient's third attack of acute gout. About two weeks had been required for his first attack to disappear (in 1941) and the second one (1944), which had been a very mild attack, had required two days to subside.

The pain element and the vasomotor phenomena of the involved joint in cases of acute gout and in cases of palindromic arthritis may have something in common. Although the 2 disease entities are quite distinct, I suspect that the mechanism of pain may be the same in both. On a previous occasion (1944) I observed a surgeon, aged 38

(Continued on page 88)

Ulcerative Colitis, Pregnancy and Delivery

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It is surprising that, with the increasing interest in ulcerative colitis and its treatment, so little attention has been paid in the literature to the occurrence of this disease and to its behavior during pregnancy and the puerperium, particularly as there is, at least in some series (Moltke,[1] Hern,[2] Kapel), a higher incidence of ulcerative colitis among women than among men. Further, it is well known that the disease is most common between the ages of 20 and 40 years; it can be assumed a large proportion of female patients have had one or more pregnancies.

This aspect has been dealt with in only one publication[3] and I have therefore paid particular attention to it while working with a relatively large series of cases (144) of this disease. The material is taken from the three medical departments of Copenhagen County Hospital, and from two medical departments of the Rigshospital (Copenhagen).

All except Bargen et al. dealt with the subject in passing.

Moltke mentioned that some women reported either that the first signs of the disease occurred, or the disease became worse, during pregnancy.

McKittrick and Moore[4] stated that a "smouldering colonic activity often lighted up by pregnancy has been an indication for the termination of pregnancy."

Kirsner,[5] Palmer, Maimon and Rickets mentioned that "in 2 patients the first symptoms first appeared during pregnancy," and of 100 patients 9 recurrences of the disease were observed during pregnancy.

Feder[6] reported that in 55 patients 5 had recurrences of ulcerative colitis during pregnancy.

Lups[7] reported a case with a severe exacerbation of the disease in the puerperium, ending in death on the twelfth day, and another case which had an exacerbation during pregnancy and aborted in the sixth month.

Bargen, Nunez and Mussey described that (1) occasionally the disease arises in the course of an apparently normal pregnancy; (2) occasionally there is complete relief of symptoms during pregnancy. Their cases consisted of 17 women between 21 and 34 years old, with a group total of 18 deliveries and 4 abortions. In 9 patients the symptoms improved following delivery, in 5 patients the symptoms became worse, and in 2 patients the symptoms remained unchanged.

Bargen considers the problem from the point of view that "some product of metabolism is present in the cases . . . perhaps a foreign protein reaction." On the other hand, the question of hormones has had to be considered (prolan, estrin, progesterone).

Apart from these papers I have found no other reference to this question.

Since my findings in my own series are not without interest on this subject, I will describe them briefly here.

There is sufficient information about 79 cases. Seventeen patients, however, first developed the disease after the climacteric; a few of these were in their fourth decade of life when they developed a fatal ulcerative colitis without an associated pregnancy.

A further 23 patients were unmarried and had never been pregnant—they were between 18 and 52 years of age. Quite a number in this age group, especially those from 18 to the mid-twenties, died, so that presumably the disease to some extent prevented marriage and pregnancy. Thus, in this group of unmarried women, 8 quite young women died of the disease, while only one older unmarried woman died (aged 48 years).

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TABLE 1

	NUMBER OF PATIENTS	REMARKS
No pregnancy	10	
Extrauterine pregnancy without exacerbation of disease	1	
Ulcerative colitis unchanged during pregnancy	4	1 patient aborted twice, in the second and third months
Ulcerative colitis improved during pregnancy	7	2 patients have been symptom-free for over six years
Ulcerative colitis deteriorated during pregnancy	11	2 patients had first symptoms of disease during pregnancy
Died in pregnancy or puerperium	5	
Pre-eclampsia	1	
TOTAL	39	

There remains a group of 39 patients who were all married and might become pregnant (Table 1). Ten patients did not become pregnant in spite of a fairly long period of marriage. One of them has been treated for sterility without effect. One patient, who had an extrauterine pregnancy, did not notice any change in the colitis during the pregnancy. Four patients observed no change in the disease during pregnancy—1 of them had 2 abortions. Thus, of the 39 women, 12 (about 32 per cent) either did not become pregnant or aborted. This is a higher sterility rate than would be expected in normal women.

Particularly interesting is the group of 7 patients who stated that the colitis improved during pregnancy; 2 of them had severe forms of the disease before pregnancy and have now been symptom-free for five years or more. In 4 the disease soon returned. One patient is now in her eighth month of pregnancy and is symptom-free after being ill for four years. In 2 patients of this group abortions had been induced previously because of the ulcerative colitis. In 9 cases the disease became worse, and in 2 it first appeared during pregnancy. The exacerbation was temporary in most, but in some it persisted after delivery.

CASE REPORTS

Case 83—A 25-year-old woman, ill for 13 years, had a severe exacerbation during pregnancy, which ended as a premature delivery, six weeks early. The deterioration has persisted for seven years.

Case 127—A 41-year-old woman had had ulcerative colitis for 13 years, with numerous admissions to the hospital. In 1944 she had a severe exacerbation of her disease during a pregnancy, and she was still not improved in 1949.

Case 142—This patient had inflammation of the bladder in the third month of pregnancy, scanty urine and swelling of the legs in the sixth month, and at the same time an increase in the symptoms of ulcerative colitis. Signs of eclampsia developed and a baby weighing 1,600 gm. was born in about the seventh month. Both mother and child survived. The ulcerative colitis was not improved.

Any possible relation between the apparent pre-eclampsia and kidney damage due to the ulcerative colitis seems very doubtful, and I have therefore not considered case 142 with the rest of the material.

In a number of cases the end of the pregnancy seemed to have caused a further deterioration in the disease, and in the next group this deterioration was so severe that the patients died (5 cases). Thus, there was a death rate of 17 per cent in the pregnancy cases. The case histories of those who died are given below:

Case 100—A woman aged 36 years had had ulcerative colitis for eight years. During a pregnancy in 1939 the disease became worse. Delivery in hospital. Pregnant again in 1940. Severe exacerbation. Developed emboli and died.

Case 98—A woman aged 26 years had been ill for 12 years. Immediately after delivery the disease became worse and led to prolonged invalidism. She was confined to bed for the last two years. Died in hospital.

Case 54—Woman aged 27 years, sister of case 52. Severe deterioration during pregnancy. Died in hospital of ulcerative colitis three weeks after delivery.

Case 12—A woman aged 34 years. Ulcerative colitis developed during puerperium in 1940, became worse during further pregnancy in 1941 and again worse in further pregnancy in 1942. Fulminant with high fever. No improvement after induced abortion. Ileostomy attempted; died in hospital.

Case 124—Woman aged 23 years. Ulcerative colitis began in the fifth month of pregnancy. Soon after delivery it became fulminant, and the patient died four weeks later.

Few diseases are so capricious as ulcerative colitis. One might therefore be inclined to say that these mortality figures are not particularly impressive and that they are only an expression of the general behavior of this disease. In 2 cases, however, the disease began during pregnancy; furthermore, the average age at death from ulcerative colitis is 43 years for men and 45 years for women. None of the present series of patients who died reached nearly this age; their average age at death was 29 years, even though one patient only developed her fatal pregnancy at 36 years of age. Thus, one cannot avoid attributing the deaths to ulcerative colitis during pregnancy.

The only material with which my series is comparable is Bargen's. He does not, however, discuss the incidence of sterility in his material. In my series the incidence of sterility was higher than one would expect, which may be due to the disease's particular character, "hardly one to encourage normal sexual activity"; and it is possible that the high proportion of unmarried women, in whom there was no likelihood of pregnancy, has the same cause. No less than 23 (30 per cent) of the women in this series were unmarried, and in many of these the disease was severe, as is shown by the mortality rate.

So far as I can find, Bargen is the only author who has reported that patients have definitely said that the ulcerative colitis improved during their pregnancies. In a somewhat larger series of ulcerative colitis patients, I found that 9 out of 143 became symptom-free for five years—this does not necessarily mean a cure—and it is notable that such a prolonged freedom from symptoms began in pregnancy in 2 out of the 39 women considered here. It is difficult to find an explanation for this. I have no doubt that those authors who nowadays believe in the psychosomatic origin of the disease would explain the recovery by the long-held wish of the patients for pregnancy and a child. In one case there was a definite psychologic factor in the disease: during the pregnancy in which the ulcerative colitis first occurred (it was partly an exacerbation) the husband left the home and the patient became completely symptom-free for the rest of the pregnancy. In another patient, who had previously been a nurse, the more regular life caused the symptoms to disappear.

The primary question is whether to advise these patients against pregnancy. Of the 39 patients to whom the question would apply, the disease did not become worse either during pregnancy or after delivery in 11, and it even improved in 7 of these. On the other hand, in 16 it became considerably worse during pregnancy and of these 5 died (the pre-eclamptic case is excluded as irrelevant to the material); these figures must affect our consideration of this question.

In my view, our position should be that in cases of ulcerative colitis the physician, and this means one with special experience in such cases, should not advise against either marriage or pregnancy unless the disease is very severe, and he should not advise against pregnancy in cases where previous pregnancies have not aggravated the disease.

If a woman with ulcerative colitis becomes pregnant the physician must insist that she come for examination at least every 14 days. Radiographs of the colon must be taken at intervals in spite of the pregnancy; proctoscopy and a hemoglobin estimation should be performed at every examination; in addition, of course, both the patient and those living with her should be asked about her condition. It is well known that some patients with this disease try to keep their condition concealed from those around them.

Further, I believe that abortion should be advised if, in spite of favorable conditions, the disease becomes even slightly worse, particularly because of the lightning suddenness with which a fatal exacerbation may develop.

The most difficult decision is in the case of a patient who desires to continue her pregnancy at any price. In this case she must be kept under very close supervision. It may be necessary to operate in spite of the pregnancy.

If a patient with severe ulcerative colitis were doubtful about completing her pregnancy, I would not hesitate to satisfy her wish for an abortion, even without an actual exacerbation. The patient's condition may deteriorate beyond help in a few days.

Quite another problem, but closely related to this one, is that of pregnancy and delivery in those who have had radical surgical treatment. Only one publication, but perhaps the best of all, deals with this question. The paper is by McKittrick and Moore, and I recommend it to anyone interested in the subject. The writers say that even if there is an ileostomy, "if the colon is quiescent and the patient has adequate insight into the problem presented, the pregnancy can be carried to term and pelvic delivery effected."

REFERENCES

1. Moltke, O.: Nonspecific, suppurative colitis and coloproctitis in connection with 117 cases. Nord. med. tidskr. 10:1704-1709 (October 26) 1935.
2. Hern, J. R. B.: Ulcerative colitis. Guy's Hosp. Rep. 81:322-373 (July) 1931.
3. Bargen, J. A., Nunez, C. J., and Mussey, R. D.: Pregnancy associated with chronic ulcerative colitis. Am. J. Obst. & Gynec. 38:146-148, 1939.
4. McKittrick, L. S., and Moore, F. C.: Ulcerative colitis. Ileostomy: problem or solution? J.A.M.A. 139:201-207 (January 22) 1949.
5. Kirsner, J. B., Palmer, W. L., Maimon, S. N., and Ricketts, W. E.: Clinical course of chronic nonspecific ulcerative colitis. J.A.M.A. 137:922-928 (July 10) 1948.
6. Feder, I. A.: Chronic ulcerative colitis: analysis of 88 cases. Am. J. Digest. Dis. 5:239-245 (June) 1938.
7. Lups, S.: Vaccine therapy in ulcerative colitis. Am. J. Digest. Dis. & Nutrition 2:65 (April); 139 (May) 1935.

LUCKHARDT MANIKIN COLLECTION UNIQUE IN UNITED STATES

SHOWN ON THESE PAGES is the manikin collection of Dr. Arno B. Luckhardt, Chicago, (opposite, right) whose collection of ten manikins is the only one in the United States, and one of the few of its kind in the world.

Although manikins such as these were designed primarily for the purpose of representing the body structures in three dimensions, they were also often made merely for artistic diversion or for the artists' patrons. One of the earliest manikins was made in 1576 although most of the figurines were made and used during the seventeenth and eighteenth centuries.

Carved in ivory, wood or marble, the manikins contain movable parts which could be used in demonstrating anatomy and particularly in practicing certain manipulations, as in obstetrics. The figurines are from 15 to 18 cm. in length, with one or both arms movable at the shoulder joint. The chest and ab-

dominal wall can be removed as one piece, showing the various thoracic and abdominal viscera, either cut out of the block or appearing as movable structures.

One of the models (shown superimposed on the other illustrations) embodies allegorical representations of the organ systems. Two tiny men are pumping up a pair of bellows for the lungs; a figure pounding an anvil with a sledge hammer (pulse) represents the circulatory system; a vat containing fermenting grapes being squeezed by a seated figure symbolizes the gastrointestinal system, the finished product of which runs into a sack held open by a small man (G. I. tract), and a cauldron enveloped in flame is used to describe the liver, then considered the hottest organ in the body.

Another method of showing the body organs in their relationship to one another was that of constructing illustrations by a method of superimposed plates, as illustrated. The plates were designed to fold back like the leaves of a book revealing successive placement of the various organs in the body.

Indications for Therapeutic Abortion

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To blot out an embryonic human life in order to preserve a mature one involves a decision of extraordinary gravity. Yet it is one which we are asked to make—or refuse—with increasing frequency today. In a few cases the facts of the matter are clear-cut and simple. But for the most part, ascertaining the exact degree of risk to the mother represented by pregnancy and balancing it against the inherent rights of the fetus is a process which may be heartbreaking in its complexity and uncertainty. It is no wonder then, that the principles, both medical and ethical, underlying such a decision are the subject of unending debate and controversy. Some obstetricians sidestep the problem entirely by refusing the performance of a therapeutic abortion under any circumstances. Others, imbued with an intense zeal for the protection of maternal welfare, call forth our censure as a result of the frequency with which they resort to the procedure.

Fortunately, the technics for the early interruption of pregnancy have become so well established that there can be little discussion regarding them. Happily, this removes one aspect of the problem from the realm of controversy. The cleavage of opinion among obstetricians stems from their personal attitudes—and they are most varied—toward the justification for the performance of therapeutic abortion. For the most part, the disagreements rest on philosophic and ethical grounds—though not infrequently differences of opinion also occur with regard to the presence or absence of specific medical risks.

To a large extent the latter results from the paucity of factual evidence, available either from the literature or the experience of any obstetric individual or group, regarding the effect pregnancy may actually have on various clinical entities. Perhaps, indeed, our very eagerness to protect maternal life and health by resorting to therapeutic abortion has helped to suppress the knowledge we should have about this relationship. This would seem to be true, for example, in heart disease, pulmonary conditions and urinary tract infections, where the greater our knowledge becomes the less concerned we are about the effect of pregnancy on these diseases.

But what do we really know, for example, about the effect of pregnancy on the convulsive central nervous system dyscrasias, or on cancer, or the aplastic anemias? While we have some information regarding the impact of pregnancy on ulcerative lesions of the upper gastrointestinal tract, our knowledge is extremely fragmentary when the lower gastrointestinal tract is involved. It is evident that there is a great need for an accumulation of authenticated experience to answer the questions of this nature which continually present themselves.

In any event, each of us carries fairly clearly in his own mind a personal attitude on which he bases his decisions on when and when not to perform therapeutic abortion. Yet it is surprising how frequently one finds that day-to-day decisions arrived at in individual cases which present continually varying facets may add up in the long run to a delineation of principles which are somewhat at variance with those which one sets up for oneself by sheer philosophic thought. It is always worthwhile, therefore, for us to examine any past performance in terms of what we *did* do as contrasted with what we *thought* we were doing. In the discussion which follows it will be our aim to be as honest as we can from this point of view.

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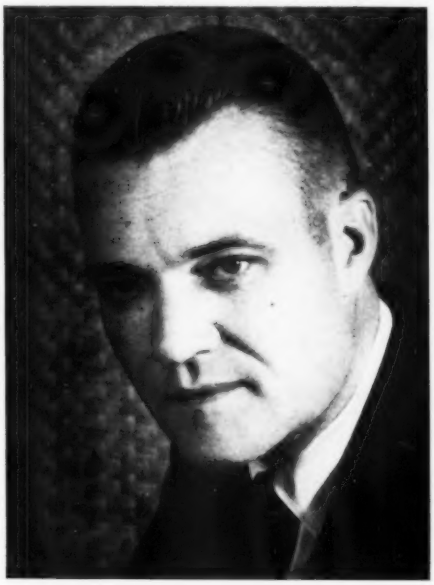


EDMUND W. OVERSTREET

A DECADE OF THERAPEUTIC ABORTIONS

During the 10 years from 1938 to 1947 inclusive, 134 therapeutic abortions were performed in the University of California Hospital. (Therapeutic abortion is here defined as the deliberate interruption of pregnancy before the twenty-eighth week.) Forty-three of these patients were under the private care of members of the obstetric staff, while 91 were clinic patients. During this same period there were 8,397 deliveries, giving a ratio of abortions to deliveries of 1:63.

It is important to point out that during this period we evolved the principle of making decisions regarding therapeutic abortion a matter for staff rather than individual consideration. All clinic candidates for this procedure are now presented to a meeting attended by six or seven full-time staff members as well as the house staff. When a physician from another department has requested therapeutic abortion for a particular patient, that department is represented at the staff meeting which considers her case. While private patients are not discussed in open meeting like clinic patients, informal consultation is always requested from at least two other staff members when the question of therapeutic abortion is at stake. Thus the decision in this question becomes a matter of group policy rather than one of individual predilection.

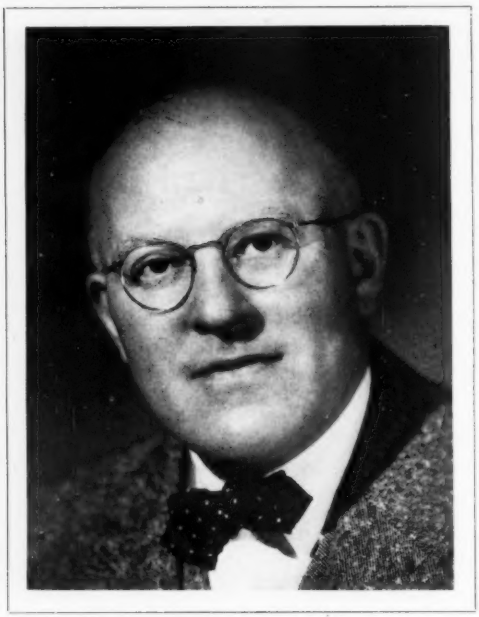
An analysis of our cases by years and by indications is presented in Table 1. The classification of indications—with slight modification—is that used by Kuder and Finn[1] in their report in 1945 of 280 therapeutic abortions at the New York Lying-In Hospital. Even though the number of our cases is small, an examination of the table reveals several interesting trends.

1. There is a steady progress toward conservatism. In spite of the constantly increasing number of obstetric patients seen from year to year in this clinic, the number of therapeutic abortions performed decreases or remains the same. This is well shown by the fact that the ratio of abortions to deliveries for the first five years of the decade was 1:37, while for the last five years it was only 1:107. The decreasing incidence of this procedure is shown graphically in Figure 1. This trend is in accordance with that presented by the recent literature, and the reasons for it should become apparent in our later discussion.

2. Toxemia—and its consequent or related conditions, chronic nephritis and essential hypertension—figures with decreasing prominence as an indication for therapeutic abortion. This is no doubt a result of our improved methods for studying and evaluating the patient from pregnancy to pregnancy. A better understanding of the etiologic and biochemical factors underlying hyperemesis gravidarum has practically ruled it out as a reason for the early interruption of pregnancy. We have not interrupted a pregnancy for this condition in the past 10 years. For other toxemias such as chronic nephritis we aborted 5 patients during the past five years while performing 5,234 deliveries, whereas in the previous five years 17 patients were aborted in the course of only 3,163 deliveries. The reasons for this change are, of course, obvious: (1) there is a steadily decreasing incidence of toxemias of pregnancy, and (2) great progress in the management of the toxemias makes it possible for us to contemplate with greater equanimity the added burden which pregnancy imposes on such patients.

3. The same trend is noticeable so far as heart disease is concerned. In spite of a two-thirds increase in our clinic population during the past five years, just one-half as many therapeutic abortions were performed in that period as during the previous five years, 7 and 14 respectively. It seems likely that in spite of the immense progress being made in the care of patients with cardiac disease, an irreducible minimum—as in the case of toxemias—will sooner or later be reached.

It must be added, however, that some clinics have apparently been able to reduce the incidence of therapeutic abortion for heart disease almost to



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the vanishing point. This is especially true of the University of Maryland Hospital where, as reported by King, Seegar and Douglass[2] in 1941, *no* therapeutic abortions for cardiac disease were performed during 6,200 deliveries. That this figure is not simply due to lack of opportunity or to inherent conservatism is evidenced by the fact that their clinic is in the "rheumatic fever belt" and that their overall incidence of therapeutic abortions is 1 per 118 deliveries.

4. Increasing doubt is being cast upon the validity of tuberculosis as an indication for therapeutic abortion under many circumstances. Most obstetricians and phthisiologists adhere today to the view expressed by Eastman[3] that if the extra work incident to pregnancy can be avoided—and here socio-economic conditions play a paramount role—pregnancy per se has no effect on tuberculosis. Therefore, it is not surprising that in our series we should find only 6 abortions performed on this indication in the past five years, whereas the previous equal period shows twice that number.

5. It is of interest that not once in the past 10 years was it found necessary to interrupt an early pregnancy because of the occurrence of acute pyelonephritis. What was once so common and deadly a condition leading frequently to this last desperate measure in its treatment has now yielded almost completely to the advances in prenatal care and the marvels of chemotherapy and antibiotics. All of our 11 therapeutic abortions for urologic indications involved chronic, long-standing or recurrent pyelonephritis complicated by permanent urinary tract damage or lithiasis. On this score it is never redundant to add another voice of appeal for eternal vigilance with regard to the incompletely treated acute urinary tract infection which becomes symptomatically silent but then as a chronic infection continues to work its progressive upper tract damage year after year.

6. The incidence of therapeutic abortion for medical diseases other than those specifically mentioned follows the same downward trend. Again, more expert management of the diseases themselves has made it possible to supervise pregnancies successfully in instances in which we would formerly have been doubtful. This is especially the case in diabetes, hyperthyroidism, rheumatic fever and acute arthritis. But this improved management has also caused us in many diseases—for example, in tuberculosis and heart disease—to revise our conceptions of just how deleterious pregnancy actually may be. In this sense we are continually being reminded of how physiologic and harmless a process pregnancy is.

7. When we come to the question of psychiatric disease we find the foregoing trends reversed. In the past five years, 6 therapeutic abortions were performed on this indication whereas the previous five years saw only 2. Unfortunately, the modern psychiatrist, for reasons which are complex and obscure, seems to request therapeutic abortion with extraordinary facility and unconcern whenever it appears that pregnancy might in any way worsen the mental illness of his patient. This—as well as the innate reluctance of most physicians to regard mental illness as a concrete disease—has made most obstetricians very hesitant to interrupt pregnancy for psychiatric indications. Nevertheless, we have gradually come to realize that in certain cases the deleterious effect of a pregnancy on mental illness can represent a definitive risk to the patient's life or a grave impairment of her future health. It seems likely that as this recognition becomes widespread we are due, for a time at least, to see a further rise in the incidence of therapeutic abortions performed on psychiatric grounds.

WHAT CONSTITUTES AN INDICATION?

TABLE 2 presents a listing of the specific indications for our 134 therapeutic abortions. Forty-eight separate medical conditions appear in this list. It is evident from this fact alone that the question of justification for the procedure is not answered by any general medical rules. It must be resolved by applying basic legal and ethical principles to individual cases.

TABLE 1
A Decade of Therapeutic Abortions

INDICATION	NUMBER OF THERAPEUTIC ABORTIONS												
	1938	1939	1940	1941	1942	5-YEAR TOTAL	1943	1944	1945	1946	1947	5-YEAR TOTAL	10-YEAR TOTAL
Toxemia (including chronic nephritis and essential hypertension)	3	3	6	2	3	**17**	0	1	2	0	2	**5**	**22**
Heart disease	1	5	3	4	1	**14**	2	3	1	1	0	**7**	**21**
Pulmonary disease (principally tuberculosis)	4	2	3	3	0	**12**	0	3	1	0	2	**6**	**18**
Urologic disease (principally pyelitis)	3	3	0	1	0	**7**	2	1	0	1	0	**4**	**11**
Neurologic disease	0	0	3	3	1	**7**	0	2	0	1	1	**4**	**11**
Psychiatric disease	0	1	1	0	0	**2**	0	1	0	4	1	**6**	**8**
Medical disease, other	0	4	3	1	2	**10**	2	2	0	0	0	**4**	**14**
Surgical and gynecologic disease	4	2	1	4	2	**13**	3	2	0	4	1	**10**	**23**
Fetal indications	0	1	0	1	0	**2**	2	0	1	0	0	**3**	**5**
Socio-economic (solely)	0	0	0	0	0	**0**	0	0	0	0	0	**0**	**0**
Miscellaneous other	1	0	0	0	0	**1**	0	0	0	0	0	**0**	**1**
TOTAL ABORTIONS	16	21	20	19	9	**85**	11	15	5	11	7	**49**	**134**
TOTAL DELIVERIES	506	573	612	703	769	**3,163**	839	880	807	905	863	**5,234**	**8,397**
ABORTIONS: DELIVERIES	1:32	1:27	1:31	1:37	1:85	**1:37**	1:76	1:59	1:161	1:82	1:123	**1:107**	**1:63**

The delineation of these principles presents one of the most difficult tasks an obstetrician may have to face.

In the state of California, for example, no one may ". . . procure the miscarriage of such woman, unless the same is necessary to preserve her life . . ." (Penal Code, Section 274). Similar statements, designed to permit therapeutic abortion, appear in the statutes of most of the states; and for the most part deliberate interruption of early pregnancy is a felony, manslaughter, under any other circumstances.*

It should be noted that the California statute, like those of most states, makes no mention of permitting therapeutic abortion simply to preserve the health of the mother. Nothing is said about the removal of an imperfect fetus. Both of these indications are condemned by omission or at least are not elucidated by specific reference. Do we adhere strictly to the letter of this vague statute? After all, the dividing line between a risk to health and an actual risk to life is often a rather nebulous one. Or are we often forced by the pressure of nonobstetric consultants as well as the demands of the general public to interpret the statute with extreme flexibility and liberality? Our cases throw some light on this matter.

A careful evaluation of our experience shows that in only 50 of the 134 patients would uninterrupted progress of the pregnancy have resulted almost inevitably in the proximate death of the mother. In the remaining 84 cases it was clear that the condition indicating therapeutic abortion would have been made considerably worse by allowing the pregnancy to continue. It was judged, after consideration, that the pregnancy would produce a grave enough impairment of maternal health as to constitute an eventual risk to maternal life. Whether such a risk truly involves the *preservation* of the life of the mother and is within the legal definition is simply a

*We are indebted to the law firm of Peart, Baraty and Hassard of San Francisco for the accuracy of the legal information here quoted.

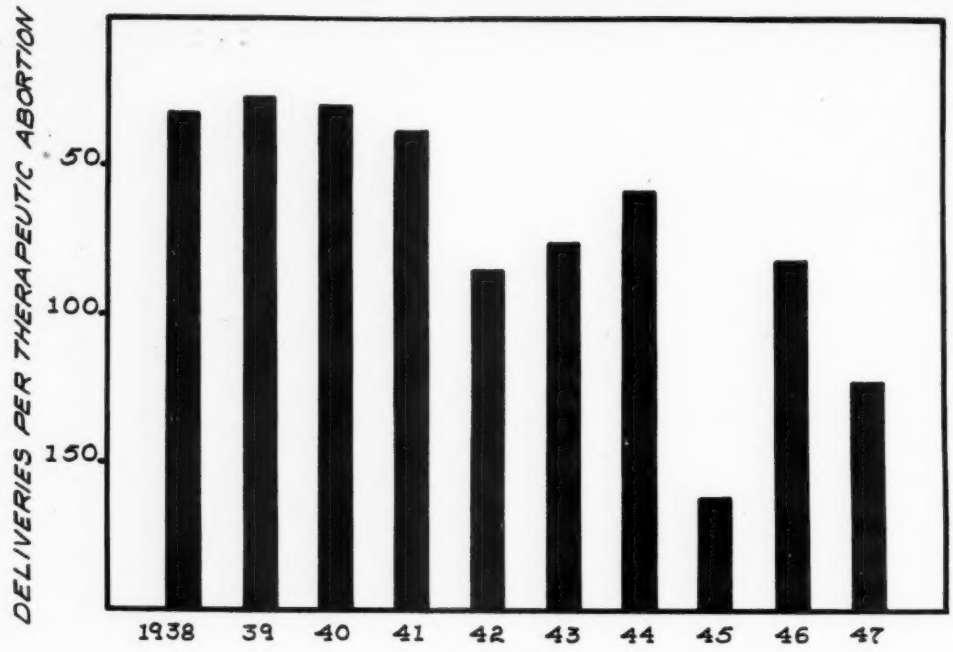

FIGURE 1

matter of interpretation of the statutes.

It must be added in this connection, however, that almost all obstetricians are constantly subjected to verbal bombardment of nonobstetric consultants who are perfectly willing to interpret the statutes even more liberally than we have done. They send us patients for therapeutic abortion in whom it is perfectly obvious that while pregnancy will undoubtedly impair the mother's health to some degree, it will in no sense constitute a risk to her life. Amicable compromise with such consultants is one of the major problems of obstetric public relations.

In connection with the legal aspects of therapeutic abortion the question of its performance for fetal indications arises. Our statutes imply that such indications are illegal by omitting any specific reference to them. Fortunately, the problem does not arise very often; but it is one which demands more satisfactory elucidation of the underlying ethical principles involved, both by the public and by the medical profession. Of our 134 therapeutic abortions, 5 were performed solely to remove a presumably damaged child, an incidence of 1 per 1,678 deliveries.

Why is it that we obstetricians tend to interpret the legal statutes regarding therapeutic abortion so liberally in the face of legal and other deterrants (dangers of the procedure, for example) which should incline us toward conservatism? The answer can only be that in doing so we feel certain that we are serving a higher ethical ideal than the law at present clearly enunciates. Otherwise our consciences would not permit us even the relatively small number of therapeutic abortions we are reporting at present.

There can be no question but that it is the duty of every modern, sociologically-minded obstetrician to strive to use this procedure in accordance with the moral and ethical principles current in the community in which he practices. Even a cursory contact with modern public and medical opinion on this matter indicates clearly that today such principles embody two specific demands which are not at present directly enunciated by our legal statutes (although recent modifications of the statutes of certain states incorporate one or both of these demands). They are: (1) insistence on the removal by therapeutic abortion of a fetus whose continued growth will result in marked impairment of the mother's health—not necessarily an immediate risk to her life, and (2) insistence

TABLE 2

INDICATIONS FOR THERAPEUTIC ABORTION, SPECIFIC DIAGNOSES

INDICATIONS	NUMBER OF CASES
Heart disease	21
Tuberculosis, pulmonary	15
Chronic nephritis	11
Essential hypertension	9
Pyelonephritis, chronic	7
Myomata uteri	5
Psychiatric (unspecified)	5
Hyperthyroidism	4
Diabetes	3
Epilepsy	3
Carcinoma, breast	3
Carcinoma, thyroid	3
Carcinoma, cervix	3
Osteomyelitis, chronic	2
Poliomyelitis residua, paralyses, crippling, etc.	2
Manic-depressive psychosis	2
Cerebral spastic paralysis, infantile	2
Previous fetal gargoylism	2
Congenital bone anomalies, mother	1
Asthma, severe	1
Previous intestinal obstruction and resection	1
Thrombophlebitis, chronic	1
Hydronephrosis	1
Tuberculosis, renal	1
Recent toxemia of pregnancy	1
Spinal fusion and chronic phlebitis	1
Previous nephrectomy following pyelitis	1
Inadvertent x-ray therapy in first month	1
Recent toxemia, impaired renal function	1
Rectovaginal fistula	1
Lupus erythematosus, disseminated, severe	1
Low grade fever, undiagnosed	1
Malnutrition	1
Herniated intervertebral disk	1
Ureterolithiasis	1
Spinal cord neoplasm	1
Congenital megacolon, previous vaginal cesarean	1
Convulsive state	1
Acute rheumatic fever	1
Hemophilia carrier	1
Bilateral ovarian cysts	1
Ulcerative colitis, chronic	1
Schizophrenia	1
Severe hemolytic anemia, mother	1
Chronic hepatitis and purpura	1
Previous anterior and posterior repair and high amputation, cervix	1
Rubella, first trimester	1
Brain abscess and spastic hemiplegia	1

TABLE 3

INCIDENCE OF THERAPEUTIC ABORTION

INSTITUTION	YEARS COVERED	NUMBER OF DELIVERIES PER ABORTION
NEW YORK LYING-IN[2]	1932-1943	167
WOMAN'S HOSPITAL, N. Y.[4]	1941	85
SLOAN[4]	1942	145
MARGARET HAGUE[4]	1931-1943 (4 done)	16,750
BELLEVUE[5]	1935-1945	76
CHICAGO LYING-IN[6]	1931-1939	195
JOHNS HOPKINS[7]	1936-1947	65
UNIVERSITY OF CALIFORNIA HOSPITAL	1938-1942 1943-1947 1938-1947	37 107 63

on the interruption of a pregnancy which presents a reasonable certainty that the fetus will be markedly imperfect.

This might seem to be merely a presumptuous judgment of our own. But a comparison of our therapeutic abortion incidence with that reported by other clinics which deal with comparable obstetric populations will show that this is not the case. Such a comparison is presented in Table 3.

If almost two-thirds of the therapeutic abortions we perform in this clinic require the most liberal interpretation of our statutes for their justification, it is fair to assume that the same is true for comparable clinics which report approximately the same incidence. Indeed, Dannreuther,[8] in a presentation of 84 therapeutic abortions at the New York Post Graduate Hospital, frankly says, "It must be admitted that, while the majority of these therapeutic abortions were done to preserve the mother's health, to prolong her life, and to prevent serious and permanent injury, under the direction of at least two licensed practitioners of medicine, the life of the mother was *not always threatened imminently*." (Italics ours.)

In spite of isolated examples of physicians who practically refuse to consider therapeutic abortion as a method of treatment of maternal disease (for example, Cosgrove and Carter[4]) the literature is filled with expressions of much the same attitude as that which we have just quoted. Furthermore, where such an attitude is not openly expressed, a careful analysis of the presented cases will reveal that it is actually operating.

The objection is often raised that unless we adhere strictly to the letter of the law, abuse of the practice of therapeutic abortion is likely to occur. There are at least two answers to this fallacious type of argument. Hodge enunciated the first answer, so far as obstetrics is concerned, as far back as 1864. In his "Principles and Practice of Obstetrics" he points out that ". . . such objections can apply to all operations in surgery; and we cannot argue against the use of a good agent simply because it may be abused." The second answer lies in the fact, already demonstrated, that our laws are not only exceedingly vague but probably do not today adequately represent the present views, or the best good, of the majority of our citizens. Even such an arch-conservative as Cosgrove—whose classical dis-

cussion of the philosophy and ethics of therapeutic abortion is a milestone in our literature on the subject—recognizes, by implication, the inadequacy of our laws regarding this matter. He says, in his portion of the discussion following presentation of this paper,[4] ". . . my plea tonight is for the profession to be specific in its own definition of its ethics and let the law follow it; let us guide the law and not be hidebound by the law."

SOCIO-ECONOMIC INDICATIONS

While a liberal approach to the use of therapeutic abortion for protection of maternal health and to protect a family from the arrival of a valueless or burdensome infant seems in general to obtain, the same cannot be said where socio-economic indications come in question. Obstetricians are still fully agreed—and rightly so—that interruption of pregnancy simply to prevent undue strain on a family pocketbook is unthinkable. This eminently moral view sometimes leads, however, to rather curious statements in the literature. The aversion to any consideration of socio-economic factors is carried to extremes in such statements as that of Dannreuther[7] that ". . . social problems and economic considerations should never influence a decision regarding therapeutic abortion to the slightest degree." This is tantamount to saying that social and economic factors have no influence on health or the progress of a disease and that they should not be taken into account in the management of it. It is obvious that the reverse is true. Indeed, in some conditions, notably tuberculosis, the social and economic situations involved may actually dictate the type of therapy the physician pursues. Similarly, socio-economic factors in the background of a prospective mother may well make the difference between a pattern of life which will permit her to carry the pregnancy with only moderate risk and one which may well put her life in jeopardy as a result of its added burden. While social and economic factors *alone* never justify interruption of pregnancy, to ignore their influence in a case under consideration for therapeutic abortion is to push the clock back to the days of medical myopia.

ROLE OF THE NONOBSTETRIC CONSULTANT

One of the curious aspects of the problem of therapeutic abortion is the fact that it is not primarily an obstetric (or gynecologic) one. Of our 134 therapeutic abortions only 25 were performed for indications strictly obstetric or gynecologic in nature or arising directly out of obstetric or gynecologic conditions. The remaining 109 indications were purely medical, neurologic, urologic, psychiatric and so on.

This puts the obstetrician in a somewhat awkward position. He becomes, in a sense, only the technician who performs the therapeutic abortion. Common sense and medical values clearly indicate that in actuality the obstetrician should never be reduced to such a low estate; yet it is undeniable that many nonobstetric consultants who request the special service of therapeutic abortion of him tend to regard him in this light. They become incensed when he takes a stand upon his legal responsibility and refuses to accede to their requests on the grounds that the abortions cannot be justified. If the nonobstetric consultant, under these circumstances, would pause momentarily to ask himself whether he is perhaps requesting the obstetrician to perform an act which might be legally interpreted as a felony, much acrimony between them might be avoided.

Indeed, many a nonobstetric consultant might be constrained to even more deliberate reflection if he were fully aware that he also, in urging therapeutic abortion upon the patient, must bear the legal responsibility for the act of therapeutic abortion—and for what the courts might possibly interpret as a felony. For the California Penal Code, like that of most states, says that "*Every* person who . . . procures any woman (to various means) with intent thereby to procure the miscarriage of such woman, unless the same is necessary to preserve her life (is guilty of a felony)." (Italics ours.)

It would also help to smooth what are often troubled waters if the nonobstetric consultant would bear in mind the fact that physicians are curious individualists. Each is jealous of his own skills and each resents any appearance of being ordered to do something by another physician. In very few consultant relationships does the physician requesting consultation ask his consultant to perform any specific procedure. Yet this approach is almost the rule when an internist or a surgeon, for example, sends a patient to an obstetrician for consideration of therapeutic abortion. It is only common courtesy to allow the obstetrician to reach his own decision—with,

of course, the consultant's information at hand—on a matter which properly falls within his domain.

Most obstetricians call to witness another reason for their reluctance to proceed with interruption of pregnancy simply on the say-so of a consultant from another field of medicine. They find all too frequently that the consultant tends to think in theoretical terms of how the pregnancy *might* affect the medical disease in question rather than in terms of what established obstetric experience has shown about how pregnancy *does* affect the disease in question. This is well illustrated by the remarks made by a physician in discussing Dannreuther's paper.[8] He said, "I am perfectly willing to recommend therapeutic abortion in a patient with rheumatic heart disease (and he went on to state the specific circumstances). You can be almost sure that as pregnancy progresses and as this living tumor increases in size and produces pressure on the diaphragm, *with a decreasing amount of thoracic space available for respiratory use. . . .*" (Italics ours.) This physician was reasoning in terms of what he *thought* happened during pregnancy, whereas all obstetricians are well aware that vital capacity increases during pregnancy up to the last month.

We find that the same attitude exists, for example, with regard to the effect of pregnancy on tuberculosis. In spite of the weight of evidence which now supports the concept that pregnancy per se is not deleterious to tuberculosis, we still find many physicians requesting therapeutic abortion almost routinely when pregnancy complicates the management of tuberculous patients under their care—and they are puzzled and often disturbed by the obstetrician's refusal to accede to their wishes.

The fact is that the obstetrician spends much of his time keeping well-informed about the effect of pregnancy on various other diseases. For the nonobstetric consultant to ask him by implication to suppress or to ignore this expert knowledge in order to bring himself to the performance of a therapeutic abortion is asking too much of any physician of integrity.

METHODS AND RESULTS

It is generally held that therapeutic abortion by any method is not without its definite dangers. Indeed, Greenhill[9] says, "We consider the operation of induced abortion one of the most dangerous in obstetrics." While we regard this, in the light of our own experience, as something of an overstatement, it seems well-established that the greater the duration of the pregnancy the greater the risks, when interruption is carried out via the vaginal route. Many of us, indeed, confess to considerable uneasiness which is absent if the interruption is carried out by abdominal hysterotomy.

It is of interest then, that of our 134 abortions, 72 or 54 per cent were performed vaginally and 62 or 46 per cent were accomplished by the abdominal route. While maternal mortality tells us nothing in this small series—since all mothers survived—it is interesting to note that maternal morbidity was 21 per cent (13 cases) for those interruptions performed abdominally, while it was only 11 per cent (8 cases) for those performed vaginally. So many added factors are involved, however, such as concurrent sterilization and duration of pregnancy, that it is difficult to know whether these figures actually represent a corresponding difference of risk for the two routes of performance.

Be that as it may, our own series demonstrates a slight but definite trend toward therapeutic abortion by laparotomy. In the first five years of the decade 41 per cent of abortions (35 out of 85 cases) were performed abdominally, whereas the figure rose to 55 per cent (27 out of 49 cases) in the second five years. Analysis of the series indicates that this difference is not due to a difference in the durations of the pregnancies interrupted during the two five-year periods.

It seems to be the result, rather, of the increasing use of concurrent sterilization (under circumstances, of course, where the indication for abortion is a permanent one). During the first five years of the series 26 out of 85 patients or 31 per cent received concurrent sterilization procedures. (This refers to deliberate sterilization; incidental sterilizations, as with hysterectomy, are excluded.) During the second five years this figure rose to 49 per cent (24 out of 49 patients). It seems clear that during the second five years whenever a pregnancy was of such a duration (approximately 12 to 14 weeks) as to make the choice of route a "toss-up," the desire to prevent further pregnancies for the patient tipped the scales more frequently in favor of the abdominal approach.

This conclusion is further borne out by the fact that in the total series of 134 therapeutic abortions 16 were repeat abortions for the same

indication. Yet no repeat abortion was performed after 1943, presumably as a result of greater care in making certain that patients with permanent indications prohibiting childbearing were permanently prevented from it.

This evidence also illustrates our feeling that the performance of tubal sterilization from below at the time of vaginal uterine emptying is a risky procedure which often leads to unexpected grief. Whenever it is possible to justify the abdominal route for this purpose, we much prefer it.

STERILIZATION AND THERAPEUTIC ABORTION

No discussion of therapeutic abortion can be engaged in without some mention of sterilization. For if we are given the moral and medical responsibility of averting risks to maternal life and health presented by already existent pregnancies, we cannot properly shirk such responsibility where future pregnancies are also concerned. It is, therefore, clear that whenever maternal disease exists of such a nature as to indicate therapeutic abortion, if the disease is a permanent one which contraindicates pregnancy at any time in the future, then sterilization should also be carried out. Under such circumstances, to interrupt the pregnancy and yet refuse to sterilize the patient is to render incomplete and unthoughtful medical care.

To be sure, it is not always a simple matter to decide whether a given maternal disease, in its future course, will always constitute a prohibition to pregnancy. But the attempt to reach this decision must always be made whenever a therapeutic abortion is contemplated, and the patient must be advised accordingly. To withhold this advice concerning sterilization is, again, to render incomplete medical care.

On the other hand, final decisions will always be made by the patient. Many such decisions will cause us, in their illogicality, to tear our hair in despair. Patients will often give ready permission for a necessary therapeutic abortion only to refuse it for an equally essential sterilization. Under such circumstances it is, of course, reprehensible to withhold the former either to bring pressure to bear to obtain permission for the latter, or because one feels that full treatment should be carried out or none at all. It is a truism to say that in medicine the whims and fancies of the patient may well impair the quality of the medical care we render. But it is always incumbent upon us to render whatever medical care we can—or to retire completely from the case if risks to the patient engendered by herself are deemed too great. For the patient who cannot bring herself to permit necessary sterilization who, however, is willing to have a current pregnancy interrupted, we can either perform therapeutic abortion without sterilization or we can refuse to accept her as a patient. The latter course would undoubtedly seem a negligent one to those of us who have the best interests of womankind at heart.

UNFORTUNATELY, our legal statutes regarding sterilization of women are, if anything, more vague, more incomplete, and more archaic than those regarding therapeutic abortion. Moreover, they show so much variation from state to state that it is difficult to discuss the matter from a national point of view. Consider, as an example, however, the California law. We quote from the paper of Peart,[10] "Vasectomy and salpingectomy under California law":

> In California there is no statute expressly granting or denying the right to perform or have performed a sterilization operation outside of state institutions. However, it would seem reasonable to conclude that, at least in so far as therapeutic sterilization is concerned, it can be performed legally under some conditions even in the absence of express permission of law. The scope of those conditions can only be ascertained or surmised by drawing analogies to similar laws. It is quite likely that the rules relating to abortions would govern since the avowed purpose to be accomplished is similar even though there is no "taking of a life" in sterilization operations.

It is evident that the same legal questions arise as in the case of therapeutic abortion, namely, the propriety of such indications as preservation of maternal health or prevention of the conception of defective offspring. Of some significance, however, is the fact that American courts seem to agree that unjustified sterilization of a woman is a lesser crime than unjustified abortion; whereas the latter constitutes manslaughter, the former is only mayhem. Both, however, are felonies.

At any rate, it is earnestly to be hoped that the medical profession will take the same lead in the modernization of sterilization statutes as the role suggested for it by Cosgrove in connection with laws regarding therapeutic abortion.

END RESULTS

We may well ask ourselves how much, in carrying out this series of 134 therapeutic abortions, we have actually limited the families of these patients. Thirty-five patients were nulliparous at the time of therapeutic abortion—though several of them had had previous spontaneous abortions, and 16 patients had had previous therapeutic interruptions. At the time of operation there already existed, for the entire group, 190 living children. This gives an overall average of 1.4 living children per family. If the 35 nulliparous patients are excluded the average is 1.9 living children for the parous patients.

The fact that maternal mortality for the series was nonexistent has already been mentioned. Overall morbidity for the series was 21 cases or 16 per cent. It should be pointed out that most of these cases represented merely a technical morbidity in the sense of a temperature rise to 38° C. or higher on any two days of the puerperium exclusive of the first 24 hours.

SUMMARY

1. A series of 134 therapeutic abortions performed during the decade 1938 to 1947 inclusive at the University of California Hospital is presented and analyzed.

2. Trends illustrated by the series include a decrease in the employment of therapeutic abortion in the treatment of toxemias, heart disease, tuberculosis and other medical diseases, with increasing use for the treatment of psychiatric disease. An overall decrease in incidence is noted.

3. A brief discussion of the legal and philosophic aspects of therapeutic abortion is presented, with a plea for clarification and modernization of our present statutes.

4. The relationship of the nonobstetric consultant to the obstetrician in the problem of therapeutic abortion is briefly discussed.

5. The relationship of sterilization to therapeutic abortion is briefly touched upon.

6. The methods and results presented by this series are as follows:

a. 54 per cent of interruptions were via the vaginal route and 46 per cent via the abdominal approach, with 11 per cent and 21 per cent morbidity respectively. A trend toward increased use of the abdominal route is noted.

b. 37 per cent of the patients received concurrent, deliberate sterilization, and a trend toward increasing use of this procedure is noted.

c. 16 repeat therapeutic abortions were performed but none after the year 1943.

d. This series includes 35 nulliparae. At the time of operation these 134 patients had 190 living children, an average of 1.4 per family or 1.9 per parous patient.

e. Maternal mortality was zero.

f. Maternal morbidity was 16 per cent.

7. A brief general conclusion is drawn regarding the need for a nationally unified body of knowledge regarding therapeutic abortion.

CONCLUSIONS

We mentioned at the outset the problem of obtaining adequate factual knowledge regarding the reciprocal relationship of pregnancy to various diseases. Our brief discussion of the legal aspects of therapeutic abortion indicates, we feel, the need for the shedding of more light on this phase of the problem of therapeutic abortion. Consideration of the present-day role of the nonobstetric consultant clearly shows the unsound and oftentimes arbitrarily personal basis for many of the therapeutic interruptions of pregnancy. The need for a collection and codification of factual material regarding this procedure is obvious—not only as a source of knowledge for the general physician but also for the benefit of obstetricians.

Such a task might, with great benefit, be undertaken by one of the national organizations devoted to the medical welfare of women, by establishing a registry of therapeutic abortions. With special emphasis on indications for the procedure and a careful follow-up summary of cases, we might in a few years accumulate a body of wisdom gleaned from the experience, intelligence and honesty of small local groups of physicians. With such a unified accumulation of factual material the profession would then be in a soundly authoritative position to "guide the law and not be hidebound by the law."

REFERENCES

1. Kuder, K., and Finn, W. F.: Therapeutic interruption of pregnancy. Am. J. Obst. & Gynec. 49:762, 1945.
2. King, J., Seegar, B. E., and Douglass, L. H.: The decrease in the incidence of therapeutic abortions. Bull. School Med. Univ. Maryland 26:145, 1941.
3. Eastman, N. J.. Ed. note. Obst. & Gynec. Survey 1:485, 1946.
4. Coscrove, S. A., and Carter, P. A.: A consideration of therapeutic abortion. Am. J. Obst. & Gynec. 48:299, 1944.
5. Perlmutter, I. K.: Analysis of therapeutic abortions, Bellevue Hospital, 1935-1945. Am. J. Obst. & Gynec. 53:1008, 1947.
6. Hesseltine, H. C., Adair, F. L., and Boynton, M. W.: Limitation of human reproduction. Am. J. Obst. & Gynec. 39:549, 1940.
7. Eastman, N. J.: Personal communication to the authors.
8. Dannreuther, W. T.: Therapeutic abortion in a general hospital. Am. J. Obst. & Gynec. 52:54, 1946.
9. DeLee-Greenhill: Principles and Practice of Obstetrics. Ed. 8. Philadelphia, W. B. Saunders Company, 1943.
10. Peart, H. F.: Vasectomy and salpingectomy under California law. California & West. Med. 54:296; 360, 1941.

Operation or Suction in Bowel Obstruction

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THERE is no controversy between conservative and operative management of bowel obstruction. They are not rival methods of therapy. They are not statistically comparable, for they are not methods which are to be employed interchangeably. Each method has its specific indications, and often the two methods are to be used in combination, to supplement each other. The indications are clear, from the standpoint of the pathologist; but the difficulty lies in the translation of the pathologic entity into a symptom complex, and the clinical recognition of that symptom complex.

All authors agree that there are absolute indications for operative therapy in bowel obstruction. These are the strangulations, the complete obstructions of the colon, and the congenital obstructions as imperforate anus and bowel atresias. Most authors agree that there are certain relative indications for operation, as the obturations of the bowel by gallstones and the like, the malignant obstructions, and those obstructions which do not respond to conservative therapy after an adequate period of trial. Furthermore, almost all authors agree that a large percentage of the simple intestinal obstructions, caused by kinks, adhesions, and plastic exudate will be resolved by conservative decompressive therapy.

It is therefore necessary only to recognize promptly those situations which require emergency operative intervention. Then, at a more leisurely pace, to diagnose those conditions which present relative indications for operation. Unfortunately this is where the difficulty rests. The diagnosis must be accurate. Yet the most experienced surgeon is beset with difficulties which tax all of his diagnostic ingenuity and experience. It is probable that in no other disease is accuracy of diagnosis as important, and as difficult.

Crowley and Winfield,[1] in discussing the diagnosis of internal strangulating obstruction, have presented a table of distinguishing features between this entity and simple acute obstruction. Yet all of the features which they discuss are relative and quantitative rather than qualitative. They would be helpful if 2 cases were side by side and were to be classified, but in the bedside evaluation, such criteria are but hints. In a previous publication,[2] I have attempted a classification by bedside methods. Yet even this has, on further experience, been only a crude guide.

Some of the criteria which I have found to be helpful are hereby enumerated. They are undoubtedly too dogmatic. Yet in the difficulties of diagnosis, some dogmatism is permissible as one is easily lost in a sea of confusion.

The first diagnosis that must be settled is whether a bowel obstruction exists. This diagnosis is based upon the history of colic (pain of a cramping nature coincident with peristaltic rushes of borborygmi), accompanied by vomiting, and/or distention, and/or obstipation. If the obstruction is high, there may be little distention, and no obstipation. If it is low, there may be little or no vomiting. If the entire bowel is obstructed by a closed loop, as in a total volvulus, there may be no distention, obstipa-

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tion, or vomiting until late in the disease. Yet in most instances, the colic will be accompanied by the full triad of vomiting, distention, and obstipation.

Once the diagnosis of bowel obstruction has been established, it must be classified into those which require urgent or emergency surgery and those which do not. Therefore we shall discuss the criteria upon which a strangulation and complete colon obstruction are discovered. The atresias will not be discussed; they are usually fairly self-evident in the newborn, and constitute a separate chapter.

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STRANGULATION BOWEL OBSTRUCTION

This lesion may be either external, as in a hernia, or internal. These may well be discussed together as they have so many features in common.

When an external hernia is strangulated, it means that its content is externally compressed at the neck of the sac. This compression affects the veins first as they are most easily collapsed. The arteries keep on filling the vascular bed, yet drainage is impossible. With the increase of capillary pressure, there is progressively hyperemia, bleeding by diapedesis, and bleeding by rhexis. In the stage of hyperemia and passive congestion, there is a transudation of fluid into the sac and edema of the bowel wall.

As the strangulation proceeds, the bowel wall becomes hemorrhagic, and then the fluid becomes blood-tinged. Even at this stage the bowel wall is usually viable, but it may well be permeable to bacteria. The pressure in the hernial content rises further. The sac becomes hard and firm. The blood flow becomes slowed and there may be thrombosis in the vessels. When the pressure has reached the point of complete stasis, gangrene supervenes.

From a clinical standpoint, bloody fluid in the sac is irritating to the peritoneum. The parietal peritoneum becomes irritated, inflamed and edematous. Therefore the sac is tender, firm, and hard. Thus the differentiation between an irreducible nonstrangulated hernia and a strangulated hernia is based upon the findings of a hard sac which is tender. Occasionally one will find solid viscera in a hernia which will simulate a strangulated one, such as an ovary, or uterus. The former will also be tender, but there will not be an obstruction.

In the internal strangulations, the situation is almost identical. The veins are usually compressed before the arteries. The process of passive congestion from hyperemia to bleeding to gangrene is the same. The confines of the large abdominal cavity, however, are not as amenable to palpation as the inguinal and femoral areas. Therefore one cannot rely on the feeling of tenseness. But tenderness is an almost invariable finding. Rebound tenderness is usually marked. Rigidity is difficult to evaluate in a distended abdomen, so is of little help. Yet careful inspection will often reveal rigidity not appreciable to the palpating hand. Abdominal respiration means that there is little rigidity. The bowel sounds soon disappear.*

Early clues in the diagnosis of strangulation are the intensity of the pain and early onset of vomiting. The x-ray film may disclose a single distended loop, usually suggestive of volvulus. There may be more or less profound shock. But the mainstays of the diagnosis are tenderness, rebound tenderness, and disappearance of bowel activity. Thus the symptoms of bowel obstruc-

*One strangulation obstruction displays no peritoneal signs: intussusception. In this form the hemorrhage is into the recipient colonic loop so that the blood appears in the stool.

FIGURE 1. Scout film of the abdomen revealing a fecalith in the appendix. This patient had the symptoms of an acute intestinal obstruction of the strangulation type with a diffuse abdominal tenderness and absent bowel sounds. There was mild distention of the small and large bowels in the scout film but the fecalith revealed the telling clue of the appendiceal origin of the peritonitis present.

tion with the superimposed symptoms of peritonitis spell strangulated loop bowel obstruction.

It is, therefore, important also to differentiate peritonitis from other causes, from strangulation bowel obstruction. This is often quite difficult. The x-ray study may be of real help. The inflammatory peritonitis will reveal distention of both the small and large intestine while the mechanical obstruction will usually show only the small *or* the large bowel distended. As most of these peritonitides are of appendiceal origin, a fecalith in the cecal area will often be discernible (Figure 1).

COMPLETE COLON OBSTRUCTION

THE other lesion which demands immediate evaluation is complete obstruction of the colon. As most of such obstructions are of the closed loop variety, being blocked at the ileocecal valve and at the obstructive site, decompression cannot be achieved by conservative means. In these, vomiting is usually at a minimum. Often the notations read "regurgitation," suggesting that only small quantities are vomited. Most of these obstructions are caused by malignancies, and the large percentage of them are obstructed at the sigmoidal or rectosigmoidal level. The patients are usually older, and often look deceptively well. Actually the diagnosis of the colonic nature of the obstruction is not too difficult as it can be made from history alone and confirmed easily by the x-ray film, or by a simple tap water enema.

Two problems beset the clinician: is the obstruction complete, and is it a closed loop obstruction? At first consideration it would appear that the completeness of the obstruction

can be determined by history alone; the passage of gas would indicate that there is some opening. But many seemingly complete obstructions can be easily converted into partial obstructions. In these the therapeutic problem is an entirely different one. In the cases of incompetent ileocecal valve, and therefore not a closed loop obstruction, much can be achieved with the intestinal tube in preparing the patient.

When the obstruction occurs in the left colon, it is usually caused by an annular carcinoma. Solid fecal material is driven into the narrowed lumen, and initiates an inflammatory reaction. The combination of narrowing, obturation, and swelling produces the blockade to the fecal stream. If one of these factors can be relieved, the complete choking will be transformed into a partial one.

To remove the tumor in the face of the complication robs one of the benefits of bowel sterilization. The edema is only reversible by means of a decompression. But the fecal obturation may often be washed away by enemas. Therefore, this is the first method to try. Almost all clysters are irritating to the intestinal tract and will cause increase of peristalsis, and drive the fecal wedge further into the malignant ring. Therefore water or oil, preferably tap water, should be used as the enema. It is not dangerous if carefully employed, as the likeliest site of pressure perforation is either the site of stercoral ulceration immediately above the malignancy or the cecum.

If enemas are unsuccessful in producing the passage of gas, and the distention is limited to the colon and no gas appears in the small bowel, a decompressive operation is imperative. How soon must the operation be performed? It is difficult dogmatically to impose a time limitation to those ancillary procedures which may make the operation safer and the anesthetic less dangerous. These are matters which are weighed in the balance of the individual surgeon's experience. The "tightness" of the abdomen, the quality of the peristaltic rushes, are contrasted to the nutritional level and the state of fluid balance, as well as the concomitant cardiac and other diseases which may be benefited by preoperative medication.

SIMPLE OBSTRUCTIONS

Simple small bowel obstructions, and these will be the lion's share, are, in my opinion, best treated by conservative measures. The use of the indwelling catheter will resolve most of them. The type of catheter is not as important as its method of employment. Most of the intestinal gas in bowel obstruction is air swallowed in the act of vomiting. Therefore, when vomiting has been stopped by a well-regulated suction mechanism, the distention should not get worse. If an intragastric tube is used, it will achieve results by emptying the stomach of gas and fluids already there and those additional fluids and gases which are returned to the stomach from the intestine by reverse peristalsis and simple equalization of intraintestinal pressure. The intestinal tubes will more rapidly secure a decompression for obvious reasons. But in the very ill patient, in whom it is difficult to pass the pylorus with a weighted intestinal tube, it is often kinder, and more efficacious, to first secure a complete and accurate gastric decompression.

In the use of the tube there are many factors which add immeasurably to the comfort of the patient. The choice of the nostril through which the tube is passed is important as one side may be narrow and partially obstructed. We also prefer to use a topical anesthetic in the nose and pharynx before passing the tube. If this is done carefully, the patient will be saved much discomfort. Adhesive tape should be strenuously avoided on the tube as it renders rubber or plastic rough and painful. The nose should be tended carefully during the time the tube is indwelling.

The tube is useful only if the lumen is patent, and if the suction mechanism is working. Often the tube does not appear to drain, and one finds either the tube clogged or the negative pressure device leaking. This demands constant vigilance.

The passage of gas by rectum is a signal that the battle has been won. At least a partial opening has been secured. But other signs of this victory are also present. The disappearance of the distention, the disappearance of colic, and the replacement of the borborygmic rush by continuous smooth peristalsis give indication that the obstruction has been relieved. If mineral oil is injected through the tube and is recoverable by a tap water enema, one may consider the obstruction cured.

A simple bowel obstruction may be converted into one with impairment of the blood supply through one of two mechanisms: The mesen-

tery may be compromised by a kink, adhesion band, or twist. Or the intraluminal pressure may become great enough with the counterpressure of the abdominal walls, to compress the venous return from the gut. Alertness for the signs of peritoneal irritation, "tenderness, rebound tenderness, and peristaltic reduction," will indicate an immediate operative intervention. The second mechanism may be prevented by adequate suction; but this may be lacking for a wide variety of technical reasons.

If the suction is ostensibly successful, yet the obstruction is not overcome, how long should one wait before relieving the obstructive mechanism by operative means? There is no definite answer to this question. We have all seen cases in which, though suction was successful, the cure of the obstructive mechanism did not take place before many days. The nutritional and fluid balance become more difficult to maintain as the days pass; the rate of thromboembolic phenomena and other complications increases as the time of conservative management increases. Therefore, there must be a time limit set upon conservative management. This time limit will vary with the cause of the obstruction and the age of the patient.

If the cause of the obstruction is an obturation by a gallstone, intervention should be performed early.* This can be diagnosed in some instances, as Rigler has demonstrated, either by a visible stone in the film, or by the presence of gas shadows in the biliary tree. In obstructions due to internal hernia, if the diagnosis can be made, the operation should also be early. Compressions of the bowel by bands, which act as hernial rings, will show little improvement with conservative measures, and should also be treated operatively after a fairly short period of decompression. The kinks, and the obstructions appearing postoperatively incident to a plastic intraperitoneal exudate do very well by conservative means, and it is in these that prolonged conservative management is indicated.

The extremes of life are not good risks for the conservative management of bowel obstruction for a prolonged period. Infants tolerate the intranasal tubes only moderately well. The aged, restricted by a catheter, are most uncomfortable and often develop complications. It is the middle age group, the young adults who tolerate the tube well. Soldiers in the last war frequently were up and about, and played cards for days with an indwelling intestinal tube connected with a suction apparatus.

*The terms of short period of suction and prolonged suction are deserving of definition. By a short period of suction is meant, in our clinic, one to three days. Prolonged suction is any period of time from three to twenty-one days.

SUMMARY AND CONCLUSIONS

Bowel obstructions may be treated either by operation or by conservative measures of intestinal suction. Actually these are not alternate methods of therapy to be used interchangeably. They are distinct methods which have their definite indications. The operative indications are intestinal strangulation, and closed loop obstruction, such as is most frequently observed in colonic obstruction. Also in those instances of congenital obstruction in which there is a complete block, intervention is indicated. Other cases may be given either brief or prolonged conservative therapy. The brief therapy should be employed for cases of obturation, internal herniation, and constrictive bands. Prolonged suction should be employed in kinks, and plastic exudate obstruction, with exception of the very young and the aged. The methods of classifying these types of obstruction have been discussed.

REFERENCES

1. Crowley, R. T., and Winfield, J. M.: Internal strangulating obstruction of the bowel. Internat. Abstr. Surg. 89:417, 1949.

2. Kouchy, J. D., and Beck, W. C.: Timing operative intervention for acute intestinal obstruction. Arch. Surg. 42:581, 1941.

Massive Gastrointestinal Hemorrhage

IN PATIENTS WITH RH NEGATIVE TYPE BLOOD

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MODERN treatment of massive gastrointestinal hemorrhage by whatever plan adopted involves multiple transfusions of blood. When catastrophic episodes of bleeding occur, the blood bank may at times be unable to supply the amount of compatible blood necessary to sustain life if the patient is of the Rh negative type. This report deals with the way in which this problem has been met.

During the past two years there have been 4 instances at the Buffalo General Hospital where massive hemorrhage from the gastrointestinal tract has occurred in patients of the Rh negative type among the 21 patients admitted with that diagnosis. The question of replacement of blood in 2 of them will be briefly outlined.

CASE REPORTS

Case 1—A white male, aged 34, with a peptic ulcer history of six years, was admitted in a state of shock. During the previous 48 hours, he had had repeated tarry stools with the vomiting of a large amount of blood just prior to admission. His blood contained 1,900,000 red cells, a hemoglobin of 5.5 gm. and was group 0, Rh negative. Transfusion of Rh negative blood was begun at once. After 2,000 cc. had been given, the pulse was still 116 per minute, of fair volume, and the red blood cells had risen to only 2,500,000 with 7.5 gm. of hemoglobin. There was no more compatible blood of the Rh negative type to be had. This man had not had transfusions prior to this admission.

After consultation it was decided that sufficient Rh positive blood should be given to prepare the patient for immediate surgery and then surgical control of the bleeding point should be effected. A total of 3,500 cc. of Rh positive blood, in addition to the 2,000 cc. of Rh negative blood previously given, was necessary to accomplish this purpose. The patient did not exhibit any reaction to the transfusions, either at the time they were given or later. The patient made an uneventful recovery and was discharged from medical observation after four weeks.

Case 2—A white male, aged 49, was admitted in a state of shock after vomiting a large amount of blood. He had had no gastrointestinal complaints, but had had tarry stools a year previously. His blood was group A, Rh negative. There was no Rh negative compatible blood available. Consequently, it was necessary to transfuse him with Rh positive blood. After 500 cc. had been given, his red blood cells numbered 3,300,000. Another 500 cc. was given without any appreciable change in red cell count or blood pressure.

The future course of this man's bleeding was at best very uncertain. We did not know at what intervals he would need further transfusion of blood. In addition, further transfusions in this patient, who had obtained Rh positive blood and had thus presumably been sensitized to the Rh factor, would necessitate the exclusive use of Rh negative blood. Instead we decided on immediate surgery, and another 1,000 cc. of Rh positive blood was given to prepare him for the operation. A subtotal gastrectomy was done and an additional 2,000 cc. of Rh positive blood was administered at that time. The resected specimen showed gastric erosions. Up to the twelfth postoperative day, no Rh antibodies were demonstrable in the patient's serum; however, these antibodies might have appeared later. At any rate, this patient too made an unventful recovery.

An important calculation has to be made in the type of cases described. The possible need for large amounts of Rh negative blood to save life has to be balanced against the fact that there is frequently only a limited supply of Rh negative blood available. This supply should be preserved for use in sensitized Rh negative male patients or in female Rh negative patients.

The only possible answer in some emergencies is to give Rh positive blood. The Rh positive blood may be given safely only for a short period of time to a nonsensitized Rh negative male before Rh antibodies appear. We consider-

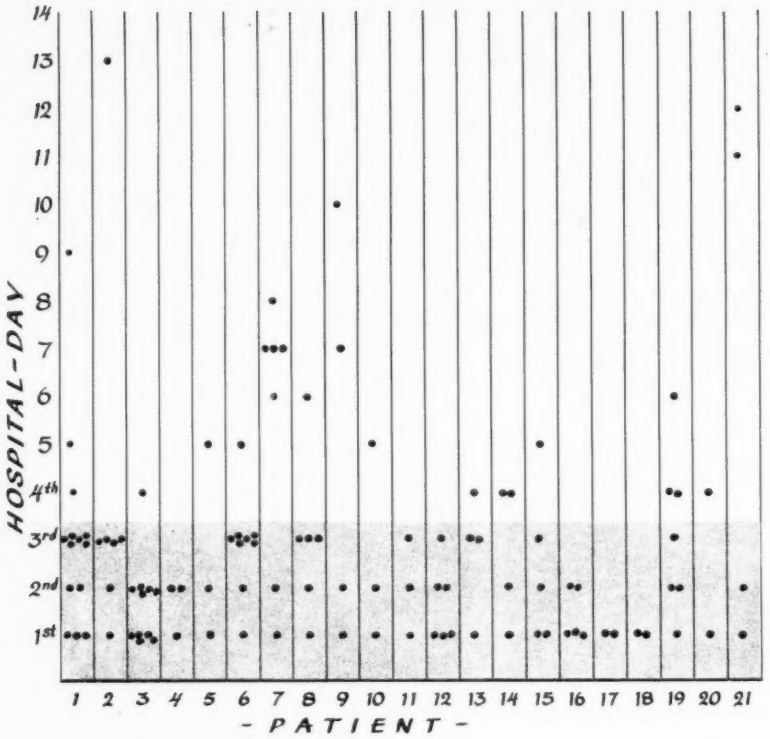

FIGURE 1. Each black dot represents one 500 cc. blood transfusion given to 21 patients with massive upper gastrointestinal hemorrhage (1948-1949) at the Buffalo General Hospital. Shaded area represents supposedly safe period during which Rh negative male patient, not previously transfused, may be given Rh positive blood. Four of this series of 21 patients were Rh negative.

ed three days rather arbitrarily as a safe period. This consideration should give pause to whomever is in charge of the patient, either internist or surgeon. If the patient is given Rh positive blood and the bleeding ceases, all is well, but if the bleeding begins again after the three-day safe period is passed, what is to be done then? Whether or not the period of three days may be prolonged we are not prepared to state at present. In other words, we would then have to give Rh negative blood exclusively.

Unquestionably the Rh negative patient with massive bleeding offers an additional weighty problem when the decision as to treatment is to be made. The internist may elect conservative treatment but, if he does so, he must be sure that sufficient Rh negative compatible blood is present in the blood bank and is likely to be there if the patient bleeds again a few days later. If it is necessary to give Rh positive blood at the outset, procrastination must not take place. The patient must be operated upon and the bleeding point secured before the three-day period is over. Certainly the fact that a bleeding patient is Rh negative may be an additional argument recommending early surgical control of the bleeding.

We have reviewed in Figure 1 how transfusions were given in all cases of massive gastrointestinal hemorrhage occurring in our hospital in the past two years. (This is the period of time during which Rh typing has been routine along with the standard blood grouping.) The number of transfusions required by these patients is represented in Figure 1. It is obvious that the largest amounts of blood were needed the first three days. Therefore, if a massively bleeding Rh negative individual, admitted in shock, desperately needing blood replacement, has to be transfused with Rh positive blood, the possibility of Rh sensitization at once becomes apparent. This offers abundant opportunity to stimulate the development of antibodies from the onset of the hemorrhage. Furthermore, 75 per cent of the patients received additional amounts of blood after the safe three-day period had passed. This affords additional opportunity for those sensitized individuals to have a transfusion reaction.

A SUMMARY

Multiple Sclerosis

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In multiple sclerosis, as in any other disease of the nervous system, two questions arise: (1) What is the nature of the lesion? and (2) Where is the lesion? It must be assumed that in multiple sclerosis a myelinolytic toxin dissolves the nerve sheaths but leaves the axis cylinders intact, at least temporarily. The end results are diffuse sclerotic patches in the brain and the spinal cord.

Multiple sclerosis is an encephalomyelitis periaxialis scleroticans. The lesion is widely scattered, disseminated, seemingly without any rule or pattern. Yet the patches show some predilection for the areas around the ventricles, so much so, in fact, that the expression "periventricular sclerosis" is justified. Sclerotic patches also occur frequently in the pons, the chiasma and the optic nerve. The papulo-macular bundle of the optic nerve is often affected. Retrobulbar neuritis results. If, in the pons, a patch is situated where the trigeminal nerve emerges, the patient may suffer from "trigeminal neuralgia." The syndrome of occlusion of the posterior inferior cerebellar artery or a Brown-Séquard syndrome may be the clinical manifestation of a sclerotic patch. Sometimes the cervical cord is affected unilaterally. The resulting syndrome may be mistaken for a spinal cord tumor. Patches of multiple sclerosis may produce the clinical picture of transverse myelitis, primary lateral sclerosis, tabes dorsalis, etc.

The patient's history is particularly important in multiple sclerosis. It may be the decisive factor in diagnosis. Sometimes it is possible to diagnose multiple sclerosis from the history alone. One must inquire meticulously about: fleeting paresthesias, dizziness, tiredness, eye symptoms (especially blurring of vision), localized paralysis or weakness and sphincter disturbances.

Fleeting paresthesias, lasting only a few days or weeks, and usually affecting one or both extremities on one side, are often seen. If these paresthesias are diffuse, the head-bending test may be helpful diagnostically: The examiner briskly flexes the head of the patient; when the test is positive, the patient experiences a feeling of electric shock in the areas where the paresthesias are localized. Intelligent patients have told me that this sensation of electric shock on head bending was the first symptom that they had noticed.

Dizziness and tiredness, particularly the latter, often occur. There are few patients with multiple sclerosis who do not complain of easy fatigability.

Eye symptoms are very common and are of great diagnostic significance. A transient retrobulbar neuritis may produce marked blurring of vision. Permanent blindness does not result. The scotomas may be for color only. The fundus may show no definite changes: "The patient doesn't see anything, and the doctor doesn't see anything." The eye affection usually heals completely, and the episode is often forgotten by the patient. Subsequent signs or symptoms of multiple sclerosis may not appear until several years after the eye incident.

Short-lived facial paralysis, affecting one side or appearing on one side after the other, or occasionally an epileptic attack may usher in multiple sclerosis. A very mild facial paralysis of a few days' duration should make one suspect multiple sclerosis.

One of the most characteristic signs of multiple sclerosis, often misinterpreted, is the so-called "useless arm." The patient complains that he cannot use one hand. Only mild pyramidal signs may be present, but they cannot account for the severity of the patient's complaints. On detailed examination one finds astereognosis—the patient is unable to recognize objects in his hand by touch. He cannot button his shirt without looking at it. Here a patch of multiple sclerosis in the parietal lobe causes central disturbance of deep sensibility and accounts for the astereognosis. In the spinal form of multiple sclerosis

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the vibration sense in the lower extremities is often diminished early in the course of the disease. This diminution is due to sclerotic patches in the posterior columns.

Generally, the diagnosis of multiple sclerosis is not difficult. The combination of fleeting paresthesias, pyramidal signs, and cerebellar signs clinches the diagnosis. In textbooks Charcot's triad—nystagmus, intention tremor, and scanning speech—is often mentioned. Invariably, the critical remark is added that this allegedly pathognomonic triad is usually not found in this disease. In fairness, one should say that Charcot himself emphasized that this triad is inconstant and late in appearance. It is difficult to condense the diversified clinical features of multiple sclerosis into any triad. The disease does not lend itself easily to any schematization. If this must be done, the following triad is, in my experience, diagnostically the most helpful and may serve as a substitute for Charcot's triad. It consists of three discrepancies.

THE *first* discrepancy, disproportion, or, let us say, incongruity, is between the objective signs and the disturbance of function. Judging from the objective signs, we expect a much greater disturbance of function than we find. The functional defect is not equivalent to the signs; the defect is much less serious than if the lesion were a macroscopic one, such as a tumor, vascular accident, etc. A patient may have definite signs of hemiplegia but still be able to use his affected hand and leg well, and may be unaware of any changes. Or a patient may have a left-sided hemiplegia of which he is aware. He does not complain about his right leg. On examination this does not show any gross functional abnormalities. The Babinski sign, however, may be positive on the right.

The *second* discrepancy lies between the severity of clinical signs on one side and the severity of constitutional or local manifestations on the other. The latter may be lacking or completely inadequate. This incongruity is seen particularly in acute multiple sclerosis or in acute exacerbations of the disease. The patient may have a severe, extensive and intensive hemiplegia, or a complete paraplegia of the lower extremities, and yet will not show corresponding constitutional or local signs and symptoms that are expected if the underlying lesion were not a patch of multiple sclerosis but a macroscopic one such as a tumor, hemorrhage, thrombosis, etc. In many instances this differential consideration has proved very helpful.

The *third* discrepancy is between the severity of the physical defects and the attitude of the patient. He simply does not have the physical complaints one would expect in view of the impairment of function. There is a peculiar lack of concern on the part of the patient regarding his disease. Patients with like functional defects arising from other neurologic conditions are much more concerned about their condition than patients suffering from multiple sclerosis. The striking indifference and aloofness of the patient toward his disease is due not so much to the euphoria, a much overplayed condition, as to the prevailing feeling of physical well being.

The clinical manifestations of multiple sclerosis can set in abruptly. Acute multiple sclerosis is a definite clinical entity, unfortunately often misdiagnosed. The patient usually improves, and often markedly so. The earlier in the course of the disease the acute attack occurs, the more violent it is, and the more circumscribed the lesion—the more likely is an improvement, and the more marked this will be. As a German proverb says, "Strong rulers do not last long."

Multiple sclerosis does not always take an up-and-down course but may progress slowly and steadily, or may become stationary at any point. I have seen a number of patients whose signs and symptoms became stationary and remained so for as long as 12 years. And yet, no one has ever been completely cured of multiple sclerosis. It is a very bad prognostic sign when a patient with long-standing multiple sclerosis and paraplegia in extension starts to have involuntary flexor spasms of the lower extremities. It is the beginning of the end, indicating a further advance toward complete interruption of function of the spinal cord.

The course of multiple sclerosis has not shown that it is definitely influenced by any of the innumerable therapeutic methods thus far applied. Transient, ephemeral success has been achieved with every method. In multiple sclerosis everything helps, and nothing helps. Remedies praised by leading neurologists a few decades or years ago are now ridiculed as utterly useless and have been completely abandoned.

The disease was first described by the Frenchman Cruveilhier in 1835. Yet now, after 115 years, the cause of multiple sclerosis is not known, nor is there any cure for this disease.

Case Report

Hydrocele of Canal of Nuck with Retroperitoneal Extension

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RECENTLY McCune[1] reviewed the literature and reported a case of hydrocele of the canal of Nuck with a large cystic retroperitoneal extension. His case was reported as the eighth of this type, with an hour-glass tumor presenting through the inguinal ring and extending into an intra-abdominal position.

Hydroceles in women are not common; an estimated 350 cases have been reported to date. The largest series has been reported by Coley[2] in 1892 with 14 cases and Counsellor and Black[3] in 1941 with 17 cases. The hydroceles occur in either groin in approximately equal proportions, and occasionally are bilateral. Frequently, there is an accompanying indirect hernia.

Regnoli,[4] an Italian surgeon, classified cystic tumors of the female inguinal canal in 1832, and his descriptions need no alteration. He described five types: (1) a diffuse hydrocele in cellular tissue enveloping the round ligament with transformation of the cellular tissue into a serous membrane; (2) an accumulation of fluid in a prolongation of peritoneum into the inguinal canal, the communication with the abdominal cavity remaining; (3) a type which differs from the second only in the fact that the pouch of peritoneum no longer communicates with the abdominal cavity; (4) an encysted hydrocele in the connective tissue about the round ligament (similar to the first), and (5) an accumulation of fluid in the remains of an old hernial sac.

Typically, the hydrocele makes its appearance in the groin as a soft reducible mass similar to a hernia. This is often present for years before the patient consults a physician and is often asymptomatic throughout its course, except for the slight discomfort produced when the cyst is presenting in the groin in the unreduced state. This type is frequently mistaken for a hernia, and an operation is usually performed for herniorrhaphy.

At the other extreme, acute abdominal symptoms can suddenly appear, or may develop at the time the patient first notices a mass in her groin. The acute symptoms are often responsible for a mistaken diagnosis of strangulated hernia, obstructed hernia, or intestinal obstruction. The acute symptoms are common in the cases with retroperitoneal extension, and were present in 5 of the 8 reported cases. Such a case was reported by Halsted and Clark[5] in 1905. Their case was a 42-year-old Negro woman, who had noted an enlargement in her right groin for eighteen years. She developed acute pain and tenderness over the mass eight days prior to admission, and had vomited twice. A preoperative diagnosis of strangulated hernia was made. At operation a cystic tumor containing 1½ oz. of fluid was found in the inguinal canal. This opened into a larger intra-abdominal cyst, which communicated with the general peritoneal cavity through a small opening.

Since inguinal hydrocele in women is so frequently misdiagnosed the condition deserves further emphasis. In the relatively asymptomatic type, accurate diagnosis is not imperative. In the cases with acute abdominal symptoms proper diagnosis is to be desired, since the conditions for which it is mistaken demand prompt surgical treatment and carry a respectable mortality.

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FIGURE 1. Note the mass in the right groin which looks like a hernia.

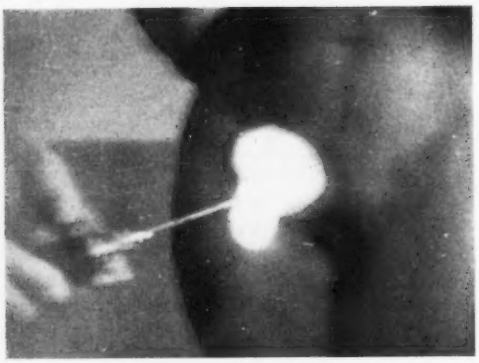

FIGURE 2. The mass transilluminates easily.

All women with a swelling in the groin should have the enlargement transilluminated, and by this simple test proper diagnosis will become more frequent. In the reported cases there were several without reference to the transillumination test, and correct preoperative diagnosis was the exception. In the case presented, the referral diagnosis was incarcerated hernia, and was not corrected until the tumor was transilluminated.

The following case is presented as the ninth case of hydrocele of the canal of Nuck with retroperitoneal extension. It is also felt justifiable as a means of emphasis for the proper diagnosis of this condition.

CASE HISTORY

A 34-year-old Panamanian female was admitted to the Station Hospital, Fort Belvoir, Virginia, on January 17, 1949, because of an acute swelling in her right groin for three days. For the past year the patient had noted a small enlargement in her right inguinal region, the size of her fingertip, which would appear when standing and disappear when lying down. Straining and coughing would also make the mass appear. This had always been easily reducible by self manipulation. Three days prior to admission the patient was lifting a basket of clothes when she felt something give way in her right groin and noticed an orange-sized mass there. The enlargement remained approximately that size and the patient had been unable to reduce it. It became progressively more painful, but there were no color changes present. She had no bowel movement and had vomited once during the twenty-four hours prior to admission. Past history was noncontributory, except for an appendectomy in 1929 and tubal ligation in 1946.

Physical examination revealed a small white female in moderate distress. Positive findings of the examination were limited to the abdomen. There was a midline suprapubic scar and a McBurney scar present. In the right inguinal region there was a firm, tender mass approximately the size of an orange. This mass was not attached to the skin, but could not be moved upon the deeper structures. It was not reducible. The mass transilluminated clearly. On pelvic examination the uterus was of normal size and position. Both adnexal regions were normal. Bimanual palpation with the external hand over the mass failed to produce any impulse to the internal hand.

A flat plate of the abdomen was negative; no evidence of intestinal obstruction was present. The urine was normal. The white blood cell count was 7,800 and the hemoglobin 16 gm.

The preoperative diagnosis of hydrocele of the canal of Nuck was made and the patient posted for operation the following morning.

At operation, the lesion was approached through a right inguinal incision with the patient under spinal procaine anesthesia. The dome of the hydrocele bulged into the wound as soon as the subcutaneous tissues were divided. The aponeurosis of the external oblique was

divided in line with its fibers. With blunt dissection the hydrocele was dissected free down to the level of the internal ring. At this point the hydrocele sac was incarcerated so that it was not reducible. The round ligament was identified and retracted from the medial side of the mass. The constricting bands at the internal ring were divided and the incarceration freed. The transversalis fascia was opened exposing the femoral vessels. This facilitated dissection into the intra-abdominal position about the hydrocele. The hydrocele sac was carefully dissected free.

Along its medial margin it was necessary to reflect the bladder wall back for a distance of 2 cm. Here there was noted a small outpocketing of the peritoneum which was taken to represent the beginning of an indirect hernia. The entire cyst and this portion of peritoneum were delivered into the wound. The peritoneum was opened and with the finger inserted into the abdominal cavity the tissues were dissected free from it. A purse string suture was then placed about the neck of the peritoneal sac and the excess peritoneum cut free, thus facilitating the removal of the hydrocele intact.

Examination of the specimen revealed the hydrocele to contain approximately 120 cc. of clear fluid. Pressure on the hydrocele would cause fluid to trickle through a small opening into the portion of the excised peritoneum, thus representing a small communication between the hydrocele and the general peritoneal cavity. The inguinal floor was repaired with interrupted black silk sutures and the incision closed.

The patient's postoperative course was uneventful and she was discharged on her ninth postoperative day.

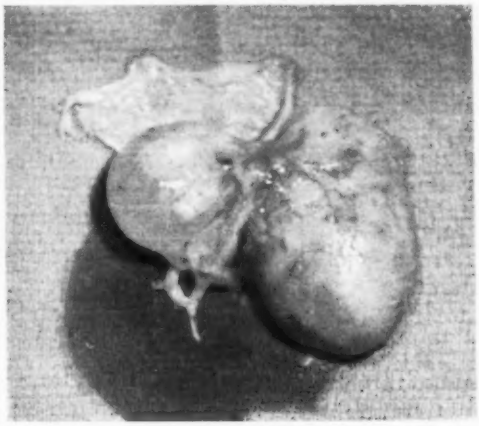

FIGURE 3. Operative specimen. Approximately one-third of the encysted portion was incarcerated superficial to the inguinal ring. The free edge of the peritoneum represents the small hernia present. There is a pin point communication present between this and the hydrocele sac.

The patient was seen as an outpatient six weeks following discharge, at which time she presented a well healed inguinal wound. She was asymptomatic and quite pleased with her operative result.

SUMMARY

1. A brief review of hydrocele of canal of Nuck is presented.

2. Proper diagnosis by use of the transillumination test is emphasized.

3. The ninth case of an hour-glass type of hydrocele in which there is intra-abdominal extension is presented.

REFERENCES

1. McCune, W. S.: Hydrocele of the canal of Nuck with large cystic retroperitoneal extension. Ann. Surg. 127:750-753, 1948.
2. Coley, W. B.: Hydrocele in the female with report of fourteen cases. Ann. Surg. 16:42-59, 1892.
3. Counsellor, V. S., and Black, B. M.: Hydrocele of canal of Nuck. Ann. Surg. 113:625-630, 1941.
4. Regnoli: Archir Generales, 1834 Tome V, Sec. II, 114 (quoted by Counsellor and Black[3]).
5. Halsted, A. E., and Clark, C. P.: Hydrocele in the female. Ann. Surg. 41:740-744, 1905.

Case Report

Local Subcutaneous Atrophy Due to Protamine Zinc Insulin Sensitivity

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Two cases of sensitivity to protamine zinc insulin have been observed. Both patients have been well controlled with insulin given as a fraction of 80 units once daily. Urine has been sugar-free and monthly blood sugars have been within normal ranges. One of the patients (case 1) has had an amputation of the right leg above the knee and has a well healed stump, with no recurrence of gangrene. Both patients have been known diabetics under treatment for some time, case 1 for three years and case 2 for two years. The patient in case 1 used 80 units of protamine zinc insulin daily and the patient in case 2 used 40 units. Insulin was taken at 7:30 A.M. daily.

Several months after protamine zinc insulin had been initiated, both patients began noticing atrophy of the subcutaneous fat with deep pitting deformities at the sites of the injections. All injections had been given by the patients themselves, in different localities, alternating sites daily. The deformities can be seen in the figures on the opposite page.

Varied efforts were made to correct this sensitivity:

1. Protamine zinc insulin was discontinued and regular insulin given three times a day. Sites of injection showed no atrophy although injections were continued over a long period of time.

2. Globin insulin was substituted. No atrophy was observed. However, case 2 couldn't be controlled. Around 4 P.M. daily she developed severe hypoglycemia, necessitating the taking of sugar. On two occasions she was admitted to the hospital in coma.

3. The brand of protamine zinc insulin was varied (Squibb's or Lilly's). Both brands caused atrophy.

4. Mixtures of regular and protamine zinc insulin were used. These gave excellent results. No further atrophy was noticeable and patients were well controlled.

5. A variation in the site of protamine zinc insulin injection was attempted. Injections were given in the skin of the lower abdominal quadrant. No definite evidence of atrophy was observed. However, this attempt was not followed long enough for definite conclusions to be made.

CONCLUSION

Local atrophy of subcutaneous tissue secondary to injections of protamine zinc insulin was observed in 2 cases. No atrophy was seen when other forms of insulin were used. Therefore, it can be concluded that the sensitivity described in these 2 cases was due to the protamine zinc fraction and not to the insulin. Protamine zinc insulin when used in mixtures with regular insulin did not produce gross atrophy. This might be explained in that there is a critical level of protamine zinc necessary to produce the atrophy described. Any amount below the critical level caused no gross atrophy.

Deep pitting deformities at sites of injection of protamine zinc insulin.

SUMMARY

1. Two cases of sensitivity to protamine zinc insulin resulting in local subcutaneous atrophy at the sites of injections are described.

2. The sensitivity was due to the protamine zinc fraction and not to the insulin. A critical level is believed to be necessary to produce the sensitivity.

3. All other forms of insulin and mixtures of protamine zinc and regular insulin did not produce atrophy.

COMING MEETINGS AND POSTGRADUATE COURSES

American College of Allergists

Seventh annual meeting, February 12-14, at the Edgewater Beach Hotel, Chicago. Section meetings will be: psychosomatic aspects of allergic diseases (Dr. Harold Abramson, New York); pediatrics (Dr. Bret Ratner, New York); allergies of the nose and throat (Dr. George Shambaugh, Chicago); allergic diseases of the skin (Dr. Rudolph Baer, New York); allergic aspects of rheumatism and arthritis (Dr. George Rockwell, Cincinnati); general session under the leadership of Dr. John Mitchell, Columbus. For information and registration write Fred Wittich, M.D., American College of Allergists, LaSalle Medical Bldg., Minneapolis, Minn.

Wayne University College of Medicine, Detroit

Postgraduate course in basic ophthalmology, 9 months, full time, beginning each year in September. For an application for the 1951-52 class, write to Postgraduate Department, College of Medicine, 1512 St. Antoine, Detroit 26

College of Medical Evangelists, Los Angeles

Annual postgraduate convention, March 11-16, at Biltmore Hotel, Los Angeles, sponsored by the Alumni Association. Dr. Paul D. Foster, general chairman. Further information may be obtained from Dr. Jerry L. Pettis, 312 North Boyle Ave., Los Angeles 33

Pediatrics

IN GENERAL PRACTICE

For general practitioners, in whose practice is included a major proportion of the medical management of infants and children, and for the specializing pediatrician as well, POSTGRADUATE MEDICINE *presents this special regular department devoted to brief discussions by recognized authorities on their preferred methods of the treatment and management of diseases and problems of infancy and childhood.*

Parenteral Fluid Therapy in Acute Illness in Infancy and Childhood

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CHILDREN'S HOSPITAL RESEARCH FOUNDATION AND DEPARTMENT OF PEDIATRICS, COLLEGE OF MEDICINE, UNIVERSITY OF CINCINNATI

DODD

NEXT to oxygen the most important substance we take into our bodies is water. Water constitutes about 70 per cent of the body weight. It furnishes a medium in which all intracellular changes take place and is the vehicle by which nutritive elements are conveyed to the cells and their waste products removed. It constitutes a large part of the blood and is necessary for the maintenance of circulating blood volume. Through its vaporization it plays an important role in the regulation of body temperature.

The average daily intake of fluid for an infant is 2½ to 3 oz. and for an older child 1 to 1¼ oz. per pound of body weight. Healthy infants usually receive sufficient fluid from breast milk or milk formulas. In fact, breast milk is designed, as one would expect, to furnish the well infant with sufficient water when he takes sufficient food. Most infant formulas are similarly designed. Older children obtain their fluids as milk, fruit juices, water, and so-called "solid foods," most of which have a high water content. A small amount is released to the body through water formed by the oxidation of foods after they are absorbed.

Water is constantly lost from the body by way of the lungs as water vapor, the skin as insensible perspiration and sweat, the kidneys as urine, and in small amounts in the stools. Most illnesses of infancy and childhood are febrile illnesses. Fever markedly increases water loss from the body. Expired air must be saturated with water vapor at body temperature. The higher the temperature of the body the more water is needed to saturate the air. Increased body temperature increases metabolism. Restlessness and convulsions often further increase metabolism, breathing, and water loss. In many febrile illnesses the respiratory center is overstimulated, the child hyperventilates and loses even more water. Forty to 50 per cent of the loss of body water may occur by way of the lungs and skin as water vapor.

The child with a febrile illness often vomits. If he vomits only once he may not lose much water, but if vomiting becomes frequent, large amounts of water may be lost. Frequent diarrheal stools may greatly enhance the child's water loss.

In many nonfebrile illnesses water loss is increased. Large amounts of water are lost by children with diabetes. Because of the high sugar content of the blood, polyuria occurs removing fluid

TABLE 1

FLUID BALANCE IN DEHYDRATION OF DIARRHEA AND RECOVERY
INFANT C. M., 19 LBS., 8 MONTHS

PERIOD (HOURS)	WEIGHT CHANGE (OUNCES)	INTAKE		URINE (OUNCES)	FECES (OUNCES)	INSENSIBLE LOSS (OUNCES)	REMARKS
		ORAL (OUNCES)	I.V. (OUNCES)				
4.6	− 9.5	8.0	0	1.0	8.2	8.2	
22.8	+ 6.0	0	41.0	2.0	18.0	18.0	Therapy started
24.4	+18.0	0	68.0	30.0	3.0	16.0	
23.7	− 0.66	10.0	20.0	22.0	0	8.0	
Estimated figures for the first 24 hours of illness if infant had received no therapy:							
24	−48.0	41.0	0	4.5	43.0	43.0	

from the body. If acidosis supervenes, as it usually does in the untreated diabetic child, water loss is augmented by the deep pauseless breathing of acidosis as well as by vomiting. Surgical conditions of the abdomen, such as congenital malformations of the gastrointestinal tract, volvulus, intussusception, incarcerated hernia, acute appendicitis, and peritonitis cause intestinal obstruction and vomiting and thus produce dehydration. Burned children lose water through the burned areas of their bodies and into the surrounding tissues.

In childhood the most acute fluid loss is caused by diarrhea and fever. The large amounts of fluid which an infant may lose by various routes in a few hours are illustrated in Table 1. The figures were obtained on an 8-month-old infant who developed a febrile illness with watery diarrhea while he was a patient on our wards.

ADMINISTRATION OF FLUIDS

The sick infant or child who is too ill to take fluids by mouth, or who persistently vomits what he takes, will have to be given fluid either subcutaneously or by vein. He will need enough to supply his daily requirements and additional amounts to make up for what he has already lost. In a hospital with good nursing care and a house staff trained to treat infants and children, the easiest way to give fluids is by continuous venoclysis. The intravenous drip must be constantly checked to see that it is running at the proper rate. Drips easily stop up or run too fast so that the calculated amount of fluid is not given or a small infant is flooded with fluid. In the average hospital it is better to give some fluid into the veins and the rest subcutaneously, intramuscularly or into the bone marrow. If large amounts of fluid are to be given subcutaneously or intramuscularly the addition of hyluronidase will help in their absorption. Hyluronidase seems to work well only at first. After the second or third day of fluid administration the tissues tend to become boggy, the fluid collects in small lakes, and remains unabsorbed.

For subcutaneous use fluids should always be isotonic with the body fluids. For intravenous administration it is advisable, particularly in infants, to use isotonic solutions as hypertonic solutions lead to diuresis and further dehydration. The best solutions to use are 5 per cent glucose in water, physiologic saline or Ringer's solution, or mixtures of varying amounts of 5 per cent glucose and physiologic saline. For subcutaneous use a mixture of equal parts of physiologic saline and 5 per cent glucose is advisable as the saline helps in the absorption of the glucose solution. If a child is markedly acidotic a 4 per cent sodium bicarbonate solution or 1/6 normal sodium lactate should be given to correct the acidosis. Sodium lactate may be given either by vein or subcutaneously; sodium bicarbonate can only be given in the veins.

Loss of water is the main cause of dehydration when the insensible expenditure of water, mostly by way of the lungs, is greatly increased as in fever and hyperventilation, with convulsions, restlessness and crying. The dehydration is the more severe the more the intake of water has been deficient. In principle, therapy should consist of the administration of large amounts of water with minimal amounts of salt-containing fluid. Water is best supplied by large amounts of 5 per cent glucose in water.

With vomiting, water, hydrochloric acid and some sodium chloride are lost. The kidneys at first conserve chloride for the body by excreting a urine low in chloride but high in bicarbonate. When renal compensation fails the chloride of the body falls and the bicarbonate rises. Restoration of fluid equilibrium requires the administration of sodium chloride solution. In addition water must be given without salt to cover the water lost through the lungs and skin and to supply the kidney with

water for excretion of accumulated waste products. Physiologic saline or 5 per cent glucose solution or a mixture of the two should be used.

With diarrhea, because of the high bicarbonate content of the intestinal juices, both chloride and bicarbonate are lost with the water in the stools. The kidneys may at first compensate for the loss by excreting an acid urine low in salt, but when kidney compensation fails the body content of salt and bicarbonate becomes low. Physiologic saline, 5 per cent glucose in water, or a combination of the two will again be needed. If acidosis is severe 1/6 molar lactate or 4 per cent sodium bicarbonate solution should also be given.

The diabetic child who has lost salt and water from the kidneys because of polyuria, and water from the lungs because of increased breathing, should first be supplied with physiologic saline and later as his blood sugar falls through the action of insulin, should receive glucose and water to supply water to the kidneys and to prevent hypoglycemia. If he is severely acidotic he should also receive enough sodium bicarbonate or sodium lactate solution to make the blood somewhat less acid.

For maintenance an infant less than a month old requires a daily intake of ¼ to ½ gm. of sodium chloride a day, an infant up to 6 months about 1 gm. and a child of 2 years 1.5 to 2 gm. Older children require 2 to 4 gm. of sodium chloride a day. If physiologic saline or Ringer's solution is used 100 cc. of the solution contains approximately 1 gm. of sodium chloride. In moderately severe diarrhea an additional amount of saline equal to 5 per cent of the body weight will be needed in the first 24 hours for replacement of lost salt and water—in severe diarrhea as much as 10 per cent. Twice as much saline is necessary with equal degrees of dehydration in cases of pyloric stenosis. In addition the infant will need per pound of body weight 60 to 90 cc. of 5 per cent glucose a day, the older child 45 to 60 cc. per pound. If hyperventilation is a feature of the illness, two or three times this amount of glucose water may be needed. If vomiting, diarrhea or hyperventilation continues the child will need additional fluid beyond his maintenance requirements each day. The type of extra fluid needed must be judged by the route by which fluid is lost.

Newborn infants and patients with pneumonia, cardiac disease, nephritis and intracranial conditions usually tolerate parenteral fluid administration poorly and should be treated with great caution using less than the calculated amounts and watching carefully for signs of pulmonary or tissue edema.

When called to treat a sick child, particularly an infant, one should always notice whether he appears dehydrated and if so, the degree of dehydration present. A careful clinical history pointed toward evaluating the portal and amount of fluid loss is essential. It is of value to inquire how many hours it is since the infant or child has voided. In the infant, signs of dehydration are a sunken fontanelle, sunken eyes and a skin which has lost its elasticity. This is most easily demonstrated on the skin of the abdomen which, when picked up, remains in sharp folds. When water has been lost without salt the skin often has a thick, doughy feel. If one watches the child's breathing one can often see that he is hyperventilating. Because of diminished blood volume and poor peripheral circulation the color of the skin is often grey and the extremities are cold and blue. The infant is lethargic or restless and irritable. He often lies with his eyes half closed. In the older child, especially if he is fat, dehydration may be difficult to recognize. The consistency of the skin and the sunken eyes are the most helpful signs.

LABORATORY TESTS

Considerable help can be obtained in assessing the amount of dehydration and the type of water loss by laboratory tests. The red count and hematocrit, often useful in adults, are seldom useful in children who tend to have lower red cell counts, often are anemic or with illness easily become so. Chemical tests of the blood serum can be very valuable. In diarrhea a decreased carbon dioxide content of the blood is usually indicative of acidosis. If the child is hyperventilating the carbon dioxide content of the blood may be low and yet the *p*H normal or alkaline. The serum chloride is an important guide in determining whether the child has lost mostly water or mostly water with salt. If the chloride is high, much glucose in water will be needed; if low much saline should be given.

The nonprotein nitrogen or blood urea nitrogen of patients without renal disease is an excellent index of the amount of water available for renal excretion and provides a rough measure of the amount of 5 per cent glucose solution needed. Infants with acute diarrhea who have for some hours been too dehydrated to void often have a serum nonprotein nitrogen as high as 100 mg. or more per 100 cc. and need several hundred cubic centimeters of 5 per cent glucose in water to hydrate them and get rid of accumulated waste products. If a child must be treated for several days by parenteral means it is well to check the blood chemistry at intervals. It must be remembered that each test measures only the concentration in the blood at that particular moment and not that in the body as a whole. Continuous clinical observation is necessary to see if the child still

appears dehydrated, is becoming edematous, or is hyperventilating.

LOSS OF SALTS

The child who becomes dehyrated loses potassium and phosphorus as well as sodium and chloride. These salts are lost from the fluid within the cells, not from the blood and the intercellular fluid. How necessary it is to give potassium and phosphorus in acute conditions and how successfully they may be restored to the cells is as yet uncertain. No signs or symptoms have been described which may be attributed to loss of phosphorus. Signs and symptoms due to potassium loss have as yet only been described in diabetes and in chronic dehydration. Until acute dehydration is overcome potassium may be high in the blood and administration of potassium salts may be dangerous. There seems little doubt that some potassium should be given in chronic cases of dehydration and starvation.

In Cincinnati we have become especially interested in the loss of calcium during dehydration. Infants with diarrhea, infants who hyperventilate because of infection or because of the administration or chance ingestion of salicylates are found to have a low level of calcium in the blood. When this happens, signs of tetany appear. The child becomes irritable, or shows irritability alternating with drowsiness. If carefully examined, ankle clonus, edema, a positive Chvostek sign and carpopedal spasm, the classical signs of tetany, may be found. Convulsions are common.

The administration of calcium is very important. Unfortunately calcium is difficult to give. If given by mouth as calcium gluconate or lactate little is absorbed. It must be given as calcium chloride and must be well diluted so that not more than 1 gm. is contained in 30 cc. of fluid. It is best given in divided doses as calcium chloride is nauseating. Two grams of calcium chloride a day is enough for a small infant, 3 for a larger one. Calcium chloride should be continued for three to four days only as its administration leads to acidosis. In emergencies calcium chloride or calcium gluconate, never stronger than in 10 per cent solution, may be given by vein. It should always be given slowly, preferably while someone listens to the heart, as calcium slows the heart and may produce cardiac arrest. To prevent the development of hypocalcemic tetany infants with severe diarrhea may be given 3 gm. or more of calcium lactate by mouth a day along with 1 cc. of dihydrotachysterol (A.T. 10).

Some drugs, particularly sulfonamides and acetylsalicylic acid or sodium salicylate, tend to accumulate in the body. They are excreted by the kidneys and if given to a dehydrated child, or one who is taking insufficient fluids, may reach dangerous levels even in doses which are usually considered safe.

Sulfonamides should not be given to a dehydrated child unless large amounts of fluids are supplied at the same time, and should not be given to any child unless one is sure that he will take fluid at the same time. The same warning applies even more strongly to salicylates.

Salicylates, even before they reach toxic levels, produce hyperventilation through their action on the respiratory center and so cause loss of water through the lungs. Severe dehydration may be seen when small doses of aspirin have been given every few hours to babies who, because of lack of appetite or thirst or because of vomiting have failed to retain fluids. Salicylate accumulates in the body, the child overbreathes, loses much water, becomes extremely dry and finally convulses. Single doses of aspirin for fever are often useful. Continuous doses may be more harmful to a sick infant than was the original disease.

Treatment of Tetanus in Children

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THE diagnosis of tetanus is seldom missed if its likelihood is considered. The question of treatment is perhaps more subject to confusion and controversy. There are probably valid differences of opinion about the total dosage of antitoxin; the type, dose, and degree of sedation that are desirable; the kinds of adjunctive therapy needed, and the amount of surgical treatment an individual case demands.

There should, however, be unanimous agreement with these therapeutic aims:

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DIETRICH

(1) to relieve and prevent tetanic spasms;
(2) to neutralize circulating tetanus toxin;
(3) to prevent the further absorption of toxin;
(4) to supply basic body needs;
(5) to refrain from causing the death of the patient through ill-advised treatment.

The following is presented as a practical plan of treatment in children which achieves the stated objectives. It is not the only workable, nor even perhaps the best theoretical regimen; however, at the Los Angeles Children's Hospital it has given results which compare favorably, on critical analysis, with any that have been published. Our series of cases is not large, but it is of sufficient size to demand attention (Table 1).

TABLE 1

GROUP	NUMBER OF CASES	DEATHS	
		Number	*Per Cent*
1 (1921-1932)	15	12	80
2 (1933-1942)	22	3	14
3 (1943-1945)	6	4	67
4 (1946-1950)	7	1	14

Group 1 received intrathecal and intravenous antitoxin and light sedation.

Group 2 received antitoxin mostly intravenously, and heavy sedation.

Group 3—a possibly unjustifiable grouping—separated because of lack of continuity of supervision during war years. Two of four deaths occurred in "bulbar reactions" following intravenous serum; one of the two recovered cases almost died from a similar reaction.

Group 4. The one death occurred 12 hours after intravenous serum in a typical "bulbar reaction."

CHRONOLOGY OF TREATMENT

Control of spasm—Once the diagnosis of generalized tetanus is suspected antispasmodic sedation should be employed before further diagnostic studies are done or any other treatment is administered. In our experience SECONAL or paraldehyde by rectum (or later by gavage) or sodium amytal intramuscularly, provides readily available and usually effective relaxation. Magnesium sulfate is not without danger. There is only one satisfactory dosage rule in tetanus; enough sedative should be given to relieve severe convulsive spasms without stopping respirations. In severe tetanus this margin is frequently very narrow.

Seconal has the advantages of rapid induction of relaxation, minimal depression of cough and gag reflexes, late interference with respiration, and rapid elimination. Sodium amytal has a more profound effect on spasms, reflexes, and respiration; paraldehyde is apparently intermediary in its effects. The administration of any sedative or combination of sedatives should be graphed on a time sheet which also indicates major seizures, so that the attending physician always has before him a

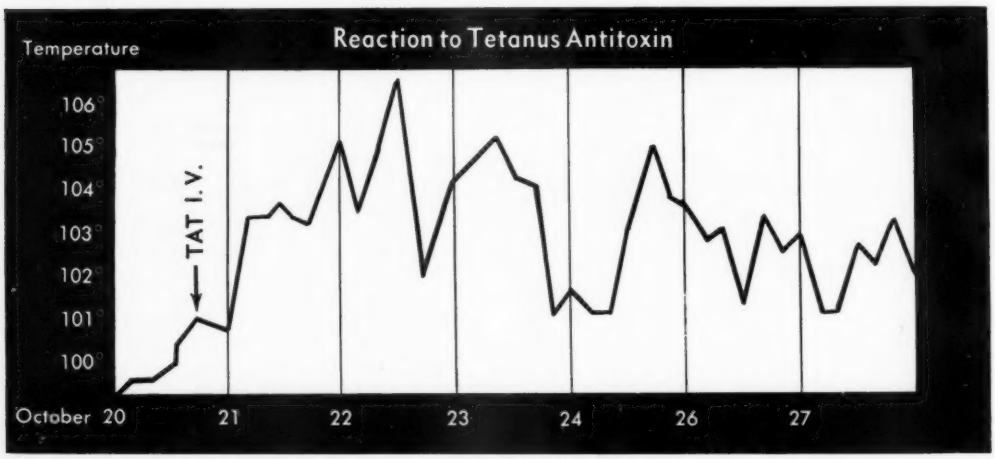

FIGURE 1. A 5½-year-old boy with mild trismus for one day. Twelve hours after entry a slow intravenous drip with 60,000 units tetanus antitoxin per day was started and continued for 48 hours. Low grade temperature of severe tetanus continued six weeks.

visual record of previous medication and its apparent effect.

Curare has been shown to be of definite value in controlling the spasms of tetanus, but its use is attended by an unremitting threat of respiratory and perhaps toxic death. It should never be used unless mechanical respirators and unusually vigilant nursing care are constantly available. These limitations render the drug more dangerous than valuable except on specially equipped hospital services, and it should be noted that deaths have occurred even when respirators has been used. We have had no experience with mephenesin.

Any sensory stimulus—auditory, tactile, thermal, or even olfactory and visual—may precipitate a severe tetanic seizure. A darkened, quiet room devoid of sudden temperature changes or air movements significantly reduces the incidence of convulsions. Provision of such an environment is therefore a major therapeutic measure.

Neutralization of circulating toxin—Soon (15 to 25 minutes) after the administration of the first dose of sedative the patient should be given tetanus antitoxin. When the child has a positive skin test to the serum or has a history of allergy, 2 to 8 minims of adrenalin chloride 1:1000 should be added to antitoxin.

The dosage and routes of administration of antitoxin have been the subject of heated debates. A small dose of antitoxin injected proximal to or around the suspected wound, and a moderate intramuscular dose should satisfy most valid theoretical considerations for neutralizing circulating antitoxin. The administration of tetanus antitoxin intravenously introduces an unnecessary risk of severe or fatal anaphylactic reaction and gains virtually nothing therapeutically. Tetanus antitoxin should *never* be given intrathecally; theoretically it is unsound and contraindicated, and practically, it not infrequently results in death in children.

Rarely after intramuscular, frequently following intravenous, and very often as a result of intrathecal serum, the patient's clinical picture will change abruptly from that of tetanus with clear sensorium and low grade or moderate fever, to one resembling bulbar disease. Hyperthermia, extreme tachycardia, very rapid respirations, relative flaccidity, and coma supervene; death may occur in 2 to 60 hours. In the occasional case that survives this reaction, the usual picture of tetanus reappears in 50 to 60 hours. Figures 1 and 2 show two illustrative charts.

Contrary to the opinions of many therapeutic enthusiasts, a total antitoxin dosage of 40,000 to 60,000 units should prove adequate. Where no primary source has been discovered it is possibly reasonable to repeat antitoxin in 4 and 8 days. In general, once the physician has administered a moderate dose of antitoxin, his time and thought are better devoted to the other aspects of treatment.

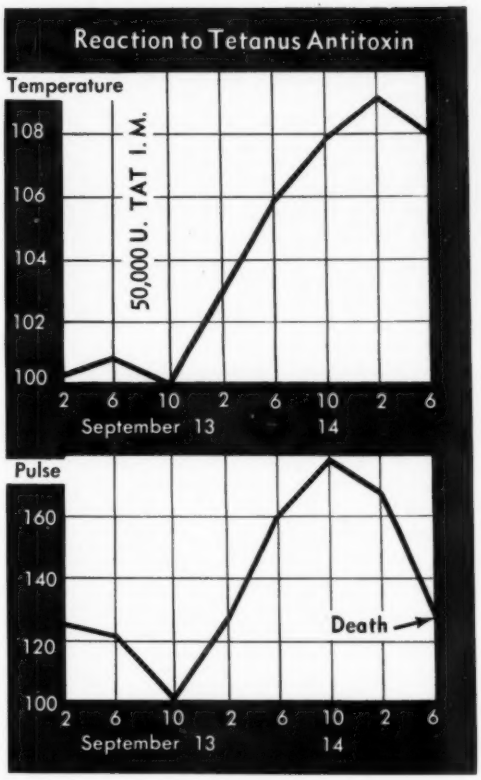

FIGURE 2. Record of a 3-year-old boy who entered the clinic with a history of one day of trismus appearing eight days after a foot injury. He was comatose, and had no convulsions during the eight hours prior to death. Death was obviously due to a reaction to serum.

Prevention of further toxin absorption—While it is vitally important to drain or extirpate the primary source of infection, the sedative and antitoxic needs of the child with tetanus should first be satisfied. Then, under deep sedation, and if needed, with supplementary pentothal or ether anesthesia, the wound should be opened or excised. In children the primary wounds are usually minor (and are completely undetectable in over 30 per cent of cases); they rarely require heroic surgery. Following the general precepts for the surgical eradication of the primary focus of tetanus we have recently removed the umbilicus in two cases of tetanus neonatorum. While both cases recovered, we can so far only say that this particular treatment is theoretically sound.

ADJUNCTIVE THERAPY

In spite of early enthusiasm, at present the use of antibiotics seems best limited to those cases in which the primary wound needs more than surgical care or in which secondary infectious complications appear. It has not been demonstrated that penicillin exerts a significant effect on human tetanus infection per se.

Intercurrent infections, and particularly those of the nose and lower respiratory tract would theoretically be best controlled without the danger of nausea by CHLORAMPHENICOL or TERRAMYCIN in customary doses.

SUPPORTIVE THERAPY

Adequate fluid and caloric intake should present no insurmountable problems. The severe stage of tetanus is usually relatively short lived, and to the best of my knowledge no child with any reasonable care has died of starvation, dehydration or electrolyte disturbance. Fluids, calories and electrolytes can sometimes be given by mouth, can generally be administered by nasal catheter to the stomach, and must only rarely be given parenterally. In the administration of fluids by gavage it should be remembered that vomiting and aspiration may occur. Any milk preparation used should be compounded to produce a soft, fine curd so that the mechanical danger of bronchial occlusion is minimized if aspiration ensues.

The nasal irritation occasioned by a permanent nasal catheter is usually less noxious than the stimuli of repeated introduction of the catheter. If it does not disturb the child, and it should not with adequate sedation, elevation of the foot end of the bed reduces the likelihood of aspiration of secretions and eructations. Suction apparatus should be continuously available, but if possible should be used only when sedation is maximal.

Finally, it is essential that recovered cases be given active immunization beginning two months after recovery.

Treatment of Infectious Mononucleosis

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McKINLAY

ALTHOUGH there is no specific treatment for infectious mononucleosis, a discussion of its management may be of interest. It should be stated that infectious mononucleosis, while established on sound hematologic and pathologic bases,[1,2] is of unknown etiology and often presents a protean clinical response and course.

It is no wonder then, that in the nearly three decades since this disease has commanded clinical attention in this country following a group of papers[1,3,4,5] featuring reports of small series of cases, various treatments have been reported as successful in shortening the course of disease or in lessening its severity and complications. Particularly since the eras of chemotherapy and antibiosis has such specific therapy been considered to benefit certain cases.

Practically all reports on therapy have been uncontrolled studies and have not, therefore, taken into account the natural variability of the course of the disease. It is well known that the disease is usually self limited and has been one of very low mortality with large series of cases reported, all with favorable outcomes. Morbidity, however, has been considerable. Often young active adults are incapacitated, sometimes for several weeks. Hepatitis or evidence of liver damage occurring in a majority of cases in the series reported adds to the severity of the illness and makes therapy more complicated.

NONSPECIFIC TREATMENT

The importance of nonspecific symptomatic treatment should not be minimized. Such treatment includes bed rest for the febrile period of illness, adequate hydration and nutrition, normal saline throat irrigations, ice collar for marked cervical swellings and tenderness, and symptomatic

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relief of headaches, body aches, and pains. The suppurative complications of the ear, paranasal sinuses, and lymph nodes are rare but must be treated on their own merits and with due regard for the principles of surgical drainage. Rarely has there occurred rupture of the spleen spontaneously or after trivial trauma with indications for surgical intervention.

The occurrence of hepatitis in a considerable number of cases, noted especially during the last decade, requires consideration of measures used in the treatment of hepatitis. It is not the purpose to attempt extended discussion of the treatment of hepatitis, but it may be mentioned that prolonged complete bed rest, forced fluids, high protein and high carbohydrate diet are advised. Intravenous glucose solution may be indicated if the patient vomits or cannot eat. Powdered foods containing a high percentage of carbohydrate protamins, vitamins, and minerals are available for tube feeding.

SPECIFIC TREATMENT

Specific treatments suggested have included the use of convalescent serum, chemotherapeutic agents, and antibiotics. With regard to the use of convalescent serum it may be stated that there is no substantial recorded evidence of its value in an adequate number of cases. Chemotherapeutic agents were used fairly extensively during the first years of their appearance. Papers advocating the use of the sulfonamides were generally those recording impressions of benefit rather than those in which there was comparison of treated and untreated series of cases. Personal impressions have not indicated noticeable benefit from such agents.

Throughout nearly three decades of observation of this disease, cases have been noted in which there was prompt subsidence of fever, sometimes with crisis-like defervescence under nonspecific therapy. This occurrence has raised doubts as to conclusions of benefit from this or that specific therapy instigated possibly as the patient began to get well.

Effect of antibiotics—A similar cycle of observations concerning the use of antibiotics has appeared. No substantial evidence has accrued that the course of infectious mononucleosis has been favorably influenced by penicillin. Its use may occasionally be justified in cases with severe edematous and exudative pharyngitis with the idea of combating possible susceptible secondary bacterial invaders and also in cases with Vincent's angina. The dosage should be adequate, that is 600,000 units or more administered intramuscularly daily and continued long enough to establish improvement or lack of benefit. Such therapy, which by and large is nontoxic, is not established on any sound etiologic basis

With the appearance of aureomycin and its apparent effectiveness in diseases presumably of viral origin such as primary atypical pneumonia and psittacosis, the use of this agent has also been suggested and tried in infectious mononucleosis because of the suspicion of its viral origin. In a relatively small epidemic observed under controlled conditions no benefit in the treated cases as compared to those receiving placebos was reported.[6] To other antibiotics is now added chloromycetin, on whose use a few isolated reports[7,8] are available, with indication of benefit in single cases. Until the place of this antibiotic is established it should be used under controlled conditions in order that premature false conclusions may be avoided. Neurologic complications, when they occur, demand treatment similar to that given for encephalitis and meningitis of nonbacterial origin.

In conclusion it may be fairly stated that while no specific therapy has as yet proved to be effective in limiting the course of infectious mononucleosis, nonspecific supportive and protective therapy has become important especially due to the frequency of hepatitis and liver damage and to the evidence of wide organ and system involvement. It is considered that sound therapeutic procedure will be enhanced if it is kept in mind that this disease is of unknown origin, practically always self limited, and of extremely variable course, sometimes with crisis-like defervescence, and that little if any importance can be attached to therapeutic conclusions reached from the behavior of an individual case.

REFERENCES

1. Downey, H., and McKinlay, C. A.: Acute lymphadenosis compared with lymphatic leukemia. Arch. Int. Med. 32:82, 1923.
2. Hovde, R. F., and Sundberg, R. D.: Granulomatous lesions in the bone marrow in infectious mononucleosis. Blood 5:209, 1950.
3. Sprunt, T., and Evans, F.: Mononuclear leucocytosis in reaction to acute infections. Bull. Johns Hopkins Hosp. 31:410, 1920.
4. Bloedorn, C. W., and Houghton, J. E.: Occurrence of abnormal leukocytes in the blood in acute infections. Arch. Int. Med. 38:413, 1921.
5. Longcope, W. T.: Infectious mononucleosis, with a report of ten cases. Am. J. M. Sc. 164:781, 1922.
6. Seifert, M. H., Chandler, V. L., and Van Winkle, Walton, Jr.: Aureomycin in infectious mononucleosis. J.A.M.A. 142:1133 (April 15) 1950.
7. Hirsch, F. G.: Infectious mononucleosis, report of a relapsing treated with chloromycetin. U. S. Navy Bull. 49:1081, 1949.
8. Lewis, P. L.: Infectious mononucleosis treated with chloromycetin. J. Pediat. 35:630, 1949.

Scientific Exhibit

Progress in Diabetes

FROM THE GEORGE F. BAKER CLINIC, BOSTON, AND THE METROPOLITAN LIFE INSURANCE COMPANY, NEW YORK

Progress in the control of diabetes has been real and substantial. Much of the accomplishment reflects the persistent efforts to bring advances in knowledge about diabetes to physicians and allied professional workers and to drive home the idea of careful and thorough education of the diabetic patient, particularly in an early stage of his disease.

Studies on the trends and prevalence of the disease demonstrate the increased frequency of diagnosis of diabetes, particularly among women, and the impact of the aging of our population on the reported frequency of the disease. The sharp reduction in the death rates from diabetes at the younger ages shows strikingly the particular significance of the discovery of insulin to young diabetics. These studies indicate the necessity for concentrated efforts in finding diabetes among middle-aged and older persons and in areas where the disease is too often missed, as shown by the low levels of the death rates in those areas.

Dietary regulation is still the basic feature of the management of diabetes. If it is to be effective, the patient needs to know the principles behind it, to acquire knowledge about foods, and to have his diet adjusted to his individual needs. If the patient requires insulin, he will do better if he knows how insulin acts, how his dosage is figured, and how by balancing his diet, insulin, and exercise he escapes both shock and coma.

Diabetic coma, while less frequent than it was, still causes far too many deaths. With modern treatment mortality is low, but this diabetic emergency can and should be wholly prevented. This is largely the responsibility of the patients themselves once they have learned how to avoid it and what to do if it impends. Likewise, careful and thorough instruction of patients in foot care will save lives and limbs and costly and prolonged hospitalization for relief of preventable foot lesions.

Physicians should have adequate preparation for the care of diabetic children, who must have special training and guidance to help them grow up to be useful, well-adjusted adults. As the child goes from the juvenile stage to early adulthood, the danger of tuberculosis must be kept in mind and suitable precautions observed. The physician can do a better job for his young patients if he has a definite goal, as well as a plan, of treatment. Juvenile diabetics eventually want to marry and have children, just as other young people do. They need intelligent counselling. Diabetic mothers and their babies will do well if the special problems of diabetic pregnancy are recognized and handled skillfully.

Arteriosclerosis in its various manifestations has become the outstanding problem in diabetes as the length of life of diabetics has increased. Vascular changes occur so much earlier in diabetics and develop so much more rapidly that the careful study of the onset and course of these conditions in diabetics should contribute much to knowledge of arteriosclerosis. Careful control of the diabetes appears to be the best means of reducing the frequency of arteriosclerosis or delaying its appearance. Any rigid proof of this is difficult, but evidence is presented which indicates the validity of this view.

Thanks largely to insulin, the gains in the average length of life of diabetic patients, and especially of the children, have been magnificent. Yet, the gap between diabetics and nondiabetics is still large. To close this gap is a challenge to medical skills in treatment and research. Physicians everywhere will take up the challenge!

This exhibit represents a cooperative project of the George F. Baker Clinic (Drs. Elliott P. Joslin, Howard F. Root, Priscilla White, Alexander Marble and Allen P. Joslin) and the Metropolitan Life Insurance Company (Dr. Donald B. Armstrong, Dr. Louis I. Dublin and Herbert H. Marks).

To provide the general practitioner, as well as the specialist with concise, readily available information on the latest, proved methods of treatment of conditions commonly encountered in an average practice, POSTGRADUATE MEDICINE *offers this department to its readers. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.*

Treatment of Parkinson's Disease

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SCHWAB

In discussing the treatment of Parkinson's disease by any method it is very important to realize that the best results of any reliable group of reported cases reach a level of only 25 per cent relief of the symptoms of the patient. This compares most unfavorably with the 90 per cent relief of symptoms effected by insulin in diabetes or prostigmine in myasthenia gravis.

There are essentially three approaches in the treatment of a patient with Parkinson's disease. The first is general support of the patient's morale and encouragement to face for the rest of his life a chronic and progressive disability and a conspicuous infirmity. The importance of this general common-sense type of psychotherapy in every case cannot be overestimated. Combined with this reassurance and encouragement, there must be a strong guidance in readjusting the life pattern on a slower time-scale that is compatible with the increased rigidity that the disease produces.

The second approach to the treatment of the disease is the use of chemical compounds which reduce the rigidity of the disease and lower the amount of tremor. There are a number of compounds in the atropine series that have been used in the past 25 years with varying amounts of partial success. In addition, there are a number of new synthetic compounds which may in certain cases produce far more dramatic degrees of improvement than the older atropine drugs.

Essentially, the problem in medical treatment of the condition involves the tolerance of side effects from the drugs used. It is possible, for example, by the injection of Hyoscine intravenously to abolish completely both rigidity and tremor, but the subject is confused, disoriented, delirious, and sleepy, and is unable to exist normally in this state. Any of the drugs if given in large amounts would produce marked benefit at the expense of strong, unpleasant side reactions. The problem, therefore, is to find a drug or combination of drugs which produces the maximum benefit in rigidity and tremor and at the same time the least possible unpleasant side effects, such as dryness of the mouth, blurred vision, confusion, and unsteadiness of gait.

It is obvious that in the treatment of this condition every patient will present an individual challenge in exquisite therapeutic balance. No results worth mentioning can be obtained by giving to all patients equal amounts of any drug with similar instruction. The individualization of the treatment

TABLE 1

DRUGS NOW IN USE IN TREATMENT OF PARKINSON'S DISEASE

NAME	COMPANY	DESCRIPTION	DOSAGE
ARTANE	Lederle Laboratories Division, American Cyanamid Company	White, scored 2 mg. tablet White, scored 5 mg. tablet	Start at ½ tablet (1 mg.) 5 times a day—approximately ½ every 3 hours—then increase slowly each dose over a period of 5 to 10 days until mild side effects occur; then reduce. The maximum dosage is 2 tablets 5 times a day (20 mg.)
PANPARNIT	Geigy Co., Inc.	Three types: sugar-coated tablets, 12½ mg.—red; sugar-coated tablets, 50 mg.—yellow; plain tablets, 50 mg.—white (double scored)	Start with 12½ mg. (1 red tablet or ¼ of white tablet) 5 times a day. Increase slowly until side effects appear; then reduce. Average dosage: 25 to 50 mg. 5 times a day. Maximum dosage: 100 mg. 5 times a day
DIPARCOL	Merck & Co., Inc.	Two kinds: 62½ mg. Diparcol A (2987); 50 mg. Diparcol B (3356). White tablets	1 tablet 3 to 4 times a day. Increase very slowly over a period of several weeks. Maximum dose is 2 to 3 tablets 4 times a day
BENADRYL	Parke, Davis & Co.	Red and white capsules, 25 mg.; also 50 mg. capsules	1 capsule 5 times a day, usually with other medicine, increasing if patient is not drowsy to 2 capsules 5 times a day—or substitute a 50 mg. capsule for the 2 capsules of 25 mg.
THEPHORIN	Hoffmann-La Roche, Inc.	25 mg. yellow tablets	1 tablet 5 times a day. Increase cautiously to 2 tablets 5 times a day until side effects appear
DRAMAMINE	G. D. Searle & Co.	Yellow scored tablets, 50 mg.	½ tablet 5 times a day, usually with other medicine. Increase cautiously to 1 tablet 5 times a day
STRAMONIUM		Grey tablet, 150 mg.	1 three times a day. Increase slowly to 1 tablet 5 times a day
HYOSCINE		Small white tablet, 0.3 mg.; slightly larger white tablet, 0.6 mg.	1 tablet 3 times a day. Increase extremely cautiously
BELLADONNA EXTRACT		Small grey tablet	1 tablet 3 times a day. Increase very slowly
TOLSEROL (Myanesin)	E. R. Squibb & Sons	Large white scored tablet, 250 mg.	2 tablets 4 times a day. Increase slowly to 5 tablets 3 times a day
PROSTIGMINE	Hoffmann-La Roche, Inc.	Scored white tablet, 15 mg.	½ to 1 tablet 3 times a day
DEXEDRINE or BENZEDRINE		5 mg. tablet	2 to 3 during morning and up to 3 P.M.

of this disease is even more difficult than that in the regulation of diabetes with insulin and diet. Unless the treatment is approached with this aspect of individualization, results with any compound will be no better than with any other.

The newer drugs, Artane, Panparnit, Diparcol, and Benadryl are the most successful. Most of these compounds are superior in patients who do not have associated vascular disease or other chronic disturbances and who have relatively stable personalities so that they adjust to the life of a handicapped person.

Panparnit is effective in reducing both rigidity and tremor. In order to be efficient, it has to be given with extra care to avoid the mild side reactions.

Artane is less effective in tremor but can be given with less care than Panparnit because of the milder side effects, and therefore in some situations it has a slight advantage over Panparnit.

Diparcol, in our experience, is effective in only a small portion of patients, but then it is superior to either of the above mentioned drugs.

From our experience, Benadryl is not effective alone, but it is very effective when combined with Artane or Panparnit.

The other compounds are not so effective and will not be discussed at this point. We have devised

a therapeutic index and a list of the drugs used in our study of 131 cases. The index and list are included here.

THERAPEUTIC INDEX FOR DRUGS USED IN PARKINSON'S DISEASE

Any patient who reports that a certain drug was the best he has had in the past, alone without other drugs, is indicated in a "+" column; and the number of such patients is multiplied arbitrarily by 4. Any report that a certain medicine is effective alone, but not so effective as the first, i.e. in second place, goes in the second column; and the number of such patients is multiplied by 2. Reports of patients that certain compounds are effective only in combination or more effective in combination go in the third column; and the number of such patients reporting is multiplied by 1, for each compound used in the combination. The total values of these columns are then added up; and this gives the positive value or assets of any individual drug.

The deficits consist of the reports of patients who found certain drugs had so many side effects that they had to be discontinued; and the number of such reports is multiplied in each instance by 4. Drugs having no effect, good or bad, i.e. indifferent, go in the fifth column and are multiplied by 2. The fourth and fifth are added together and form the deficit. Assets are divided by the deficits; and this quotient I have arbitrarily called the Therapeutic Index. The order of this index comes as follows:

Artane	3.1	Hyoscine	0.3
Panparnit	2.8	Rabellon	0.3
Benadryl	2.0	Dramamine	0.2
Stramonium	0.8	Prostigmine	0.2
Thephorin	0.6	Dexedrine	0.2
Diparcol	0.5	Benzedrine	0.2
		Tolserol	0.1

Surgery of the brain is a third approach to the treatment of Parkinson's disease; although it has been done by a number of surgeons for this disease, up to the present time it has produced very little sustained improvement.

Treatment of Rheumatoid Arthritis

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THE etiology of rheumatoid arthritis is unknown. Its treatment until the present time has been purely empiric. Due to its chronicity, prevalence, and production of marked deformities and disabilities, it has long been a bugaboo to the medical profession. As a result, the average physician has accepted a very pessimistic outlook as to its curability and relief.

Rheumatologists have recognized for some years that this type of arthritis is a disease involving the entire body and that the joint pathology is only one manifestation. They have recognized the importance of treatment of the individual as a whole, with special emphasis on treatment of the joints. To treat it only as a disease of the joints is a mistake.

The treatment of rheumatoid arthritis can be divided into general and specific measures. Our experience has been that the patients in the poorest physical condition when first seen were those in whom we could expect the best results. From this we concluded that any measures which improved the patient's general health also improved his arthritis.

General measures of proved value in the treatment of rheumatoid arthritis are: attention to nutrition, correction of anemia, relief of pain, maintenance of joint mobility, prevention of deformities, preservation of muscle strength and tone, and psychotherapy.

There is no specific diet in the treatment of this disease. The patient should be encouraged to eat a nutritious, well-rounded diet. Special emphasis should be placed on the taking of foods high in protein content such as lean meat, eggs, milk, cheese, and lentils. Extra feedings are usually necessary in the active phase of the disease. Multivitamin capsules, with or without iron, should be added to the diet.

Anemia invariably accompanies active rheumatoid arthritis. It responds poorly to iron and liver therapy. Transfusions of fresh whole blood are an invaluable aid in the correction of this anemia. They also supply much-needed protein, give the patient a sense of well-being, improve his general resistance, and materially shorten the active phase.

Transfusions should be given as often as required to maintain the patient's blood count near

a normal level. We have given as many as 25 to 30 pints of blood to patients over a two-year period. Four to eight are commonly required for any particular active phase. Great care must be taken to avoid reactions due to incompatibility and to avoid using blood which may contain the virus causing hepatitis.

Relief of pain is of paramount importance to the patient. Due to the chronicity of the disease, care must be used in the selection of analgesic drugs. In our experience, aspirin is the most effective, safest, and cheapest. We ordinarily give 2 or 3 tablets on arising, at noon, evening, and at bedtime. Extra doses may be given if necessary. The addition of ¼ to ½ gr. of phenobarbital to any or all of the doses of aspirin increases the strength and duration of the analgesia.

The judicious use of heat in any form to the affected joints is of great benefit in helping to relieve pain and maintain joint mobility. Heat may be used in the form of hot baths, hot packs, hot water bottle, electric heating pad, or infrared lamp. We have found hot wax to be especially useful in controlling the painful, swollen, stiff finger, hand, and wrist joints. Heat is most useful if of only moderate intensity, maintained for periods of one to two hours, and repeated three to five times daily. If the heat is too intense or prolonged, discomfort and restlessness may actually be increased.

During the acute phase of the arthritis mobility must be maintained by daily passive motion of each affected joint through as full a range of motion in all planes as can be tolerated by the patient. Active motion, "exercises," and weight bearing should be discouraged during the active phase. Rest of the affected joints and of the entire body is of prime importance.

It is very important to prevent deformities. The patient must be observed frequently and any tendency toward flexion deformities must be counteracted at once. It may be necessary to use split casts, splints, or braces during a part of the day or night. In this connection, the counsel and advice of a competent orthopedic surgeon is invaluable. If deformities have occurred, active orthopedic treatment with the use of corrective splints, braces, or surgical procedures should be carried on by a competent, interested orthopedic surgeon after the disease has become quiescent.

One of the outstanding features of rheumatoid arthritis is the marked muscle atrophy which takes place. This must be prevented insofar as possible by the use of daily gentle muscle massage. If this attention to the muscles is neglected, there may be such loss of strength and tone that the patient is unable to properly manipulate the joints even after the active arthritis is relieved.

The massage should be given to all the major muscle areas of the body. A member of the family should be instructed by the physician in the correct manner of giving this gentle massage. This is not only more economical for the patient, but a member of the family is less likely to do harm by too-vigorous massage than an improperly trained or disinterested professional masseur. The massage and manipulations should be of such gentleness that pain, discomfort, or fatigue do not persist for more than one hour thereafter.

Most of the patients are depressed, have endured a great deal of pain, and are very apprehensive as to what the future holds in store for them. A pessimistic attitude on the part of the attending physician is most distressing to them and certainly inhibits their ability to improve. We believe that giving the patient reassurance is one of the great helps that he has in enduring a rather long, painful, and disabling illness. Any case of rheumatoid arthritis that is watched carefully and treated judiciously over a period of time will improve.

SPECIFIC MEASURES

There is not at this time any generally available specific treatment for rheumatoid arthritis but there are various so-called specific measures which have been in general use from time to time. Serums, vaccines of all types, bee venom, foreign protein injections, fever therapy, x-ray, and massive doses of vitamin D have all been discarded by informed rheumatologists. They are not only of no benefit but often lower the patient's resistance and may aggravate the condition or even produce new complications.

The wholesale eradication of presumed foci of infection has been greatly overdone. We do not go over these patients with a microscope in a minute search for foci of infections. However, if they do have periapical abscesses, marked pyorrhea pockets, badly infected tonsils, pus in the paranasal sinuses, or infection in the prostate gland or elsewhere, these conditions are corrected by appropriate treatment in the same way and for the same reasons that they would be for any other patient. A time should be chosen for the treatment of these local infections when the patient is in the best possible general physical condition. Penicillin should be given during the period of active surgical treatment of such local infections.

Small oral doses of estrogenic substances given to women with rheumatoid arthritis at the time of the menopause are beneficial in that they improve their sense of well-being and emotional attitude. However, they probably have no direct effect on the arthritis itself.

Gold therapy is generally conceded to be of great value in the treatment of selected cases of rheumatoid arthritis. It should not be used until after the patient's general health and resistance have

been improved to the greatest extent possible by the various measures previously described. It should always be considered as an adjuvant to these other measures, and not as a "specific" treatment to be used alone.

We use gold sodium thiosulfate with an initial dose of 10 mg., increasing 5 mg. each week until a dosage of 35 mg. is reached. This amount is given each week for thirty weeks, and is followed by a rest period of one month. Thereafter, 35 mg. are given at monthly intervals for six to twelve months. At this time its use is discontinued if the disease is quiescent or the weekly schedule is reinstituted if activity continues or recurs.

Gold salts should always be given intramuscularly. The patient should be carefully observed for signs of sensitivity or toxicity. During the time that gold is given, the patient should be instructed to watch for nausea, vomiting, itching of or a rash on the skin, polyuria and diarrhea. If any of these symptoms occur without other obvious explanation, the use of gold should be discontinued. The physician should do a complete blood count and urinalysis every four to eight weeks.

Gold therapy is not the final answer in the treatment of rheumatoid arthritis but its use should be seriously considered for those patients who have failed to respond satisfactorily to the various other measures that have been described.

Cortisone, or Compound E, and ACTH are very beneficial in the alleviation of symptoms and signs of rheumatoid arthritis. The use of these substances has been largely restricted to experimental research in a few large clinics because of their great scarcity and expense. They are now more generally available, but their final applicability is still to be evaluated.

The effects of these substances have already demonstrated that all the pathologic changes in rheumatoid arthritis are not necessarily irreversible. They also indicate that the fundamental pathology is probably biochemical rather than infectious in nature and support the thesis that treatment should be directed toward the whole person rather than to the joints alone. Exactly what these substances will do for the treatment of this disease in the future is not known, but they do show us that it can respond in a big way to therapy. We must use the means now at hand until these or other materials become available to us.

The Gingiva in Pregnancy

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The gingivae of 530 pregnant women (between the ages of 16 and 40 years) were examined,[1] and the following conditions were found: 44.6 per cent of the women presented no pathologic changes; 35.9 per cent showed mild gingivitis; 17.5 per cent showed moderate gingivitis; 1.5 per cent showed severe gingivitis, and 0.5 per cent showed "tumor" formation. When these data were compared with those of nonpregnant individuals, it was found that no significant difference in incidence of gingival changes existed between the pregnant and nonpregnant women.

Clinically, gingivitis in pregnancy is characterized by localization of the inflammation to a few gingival papillae which show a rather sharp demarcation from the attached part of the gingiva. The edges of the gingival margins are often red, fringed, and swollen, and appear sharply demarcated from the attached gingiva, which is pale and firm. Hyperplastic papillae tend to show considerable overgrowth and have been wrongly classified as tumor formations. Histopathologic investigation of gingival biopsy specimens show that gingivitis in pregnancy is characterized by a proliferative tendency.

Treatment should be prophylactic; a clean mouth should be maintained through proper oral hygiene. Patients with healthy gingivae and clean mouths do not develop gingivitis during pregnancy.

If gingivitis has developed, instrumental cleaning of the teeth, medication with mild astringents, and application of oxygen are indicated. The patient is instructed in a regimen of vigorous home care.

In cases of extreme hyperplasia which interferes with esthetics, phonetics, or chewing, we may resort to surgery (gingivectomy). This should be done especially if gingival hyperplasia occurs at an early stage of pregnancy. If it occurs late, surgery may not be needed, because a few weeks after pregnancy the oral symptoms become greatly reduced or completely disappear. Sometimes surgery

has to be performed after pregnancy.

If treatment has to be rendered, it should be carried out, but the phase of pregnancy and degree of gingival inflammation should be considered. Treatment should not be delayed because of pregnancy, but it may need to be modified.

Gingivitis in pregnancy has a local irritative origin, modified by the systemic disturbance. Pregnancy may be considered a conditioning factor which influences the character of the inflammatory reaction. Pregnancy is not, however, to be considered the primary etiologic factor in gingivitis in pregnancy.

[1]MAIER, A. W., and ORBAN, B.: Gingivitis in pregnancy. Oral Surg., Oral Med. & Oral Path. 2:334-373, 1949.

Treatment of Ankle Sprain

WITH SPECIAL REFERENCE TO THE USE OF ETHYL CHLORIDE SPRAY

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ANKLE sprain is probably the most common orthopedic injury. Methods of treatment are varied, but most of them produce good final results. However, some types of therapy restore the patient to normal activity sooner than others and these should be utilized whenever possible. It is the purpose of this paper to review the treatments of ankle sprain and to present a method which the author believes to be the simplest and most effective treatment for most ankle sprains.

CLASSIFICATION OF SPRAINS

The incomplete tear—In the vast majority of ankle sprains the ligaments involved are only slightly damaged and will be healed by relatively short periods of support to the ankle joint. It is this type of injury that this paper will discuss.

The complete tear—In 5 to 10 per cent of ankle sprains, however, damage is so severe that one or more of the three lateral ankle ligaments is completely torn through (Figure 1). The anterior talofibular ligament is the most important of this group and is the one most often injured. Proper identification of these cases is difficult without the aid of special diagnostic procedures.

All severe ankle injuries with marked swelling, discoloration and pain should be examined and x-rayed under anesthesia to determine whether one or more of the lateral ligaments is completely torn. This condition allows an unusual amount of inversion of the foot (Figure 2). In such instance treatment must include plaster immobilization of the ankle joint for a period of approximately six weeks.[1,3] If inadequate immobilization is prescribed for these cases of complete rupture of the lateral ligaments, an unstable joint and prolonged disability will result.

TREATMENT OF INCOMPLETE TEAR OF ANKLE LIGAMENTS

Adhesive strapping—Until the last decade the treatment for ankle sprain was almost stereotyped, consisting of bed rest or crutches, hot applications, salicylates and adhesive strapping after the method first described by Gibney.[4] With this treatment most sprains healed satisfactorily but relatively long periods of disability was the rule.

Procaine infiltration—Some 15 years ago Leriche,[5] Arnulf[6] and others of the French school introduced an ambulatory treatment of ankle sprain that greatly decreased disability after this injury. This treatment was based on the principle of injection of a local anesthetic into and around the painful area of the ankle. After the pain was relieved the patients were encouraged to walk with full weight on the injured member and found that walking was entirely possible. Many individuals so treated were able to resume their normal activities immediately with little or no discomfort.

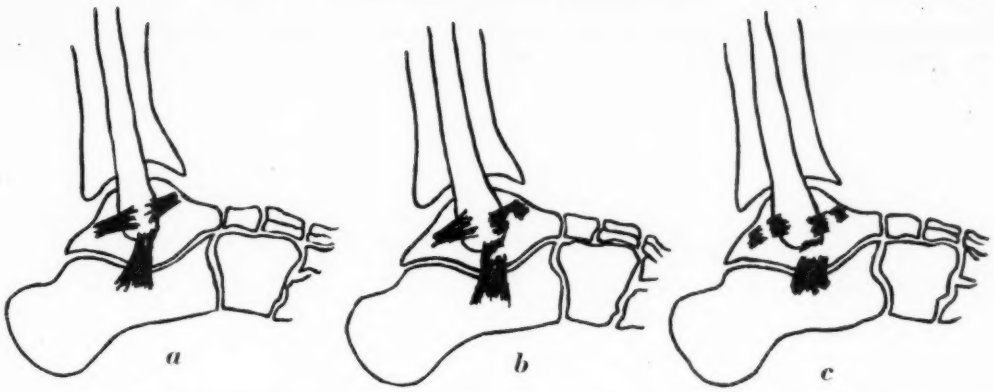

FIGURE 1*a*. Lateral view of ankle ligaments illustrating normal anterior talofibular, posterior talofibular and calcaneofibular ligaments; *b*, the usual ankle sprain; *c*, complete tear of all lateral ankle ligaments.

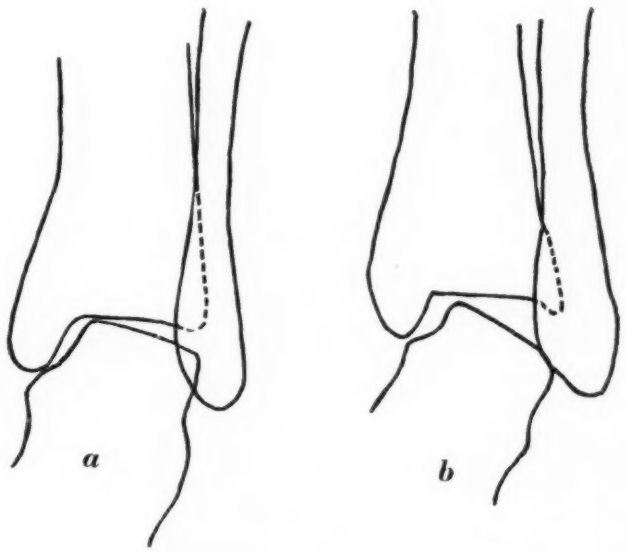

FIGURE 2*a*. Drawing of x-ray in anterior-posterior view with the ankle in forced adduction of incomplete tear, and *b*, complete tear of the lateral ankle ligaments.

The work of Leriche and Arnulf was immediately subjected to intensive scrutiny by our army and navy surgeons who were anxious to return injured men to duty as soon as possible. Bakst,[7] McCormick,[7] Webber,[8] McLaughlin[9] and others found in a very high percentage of cases that the men could return to duty immediately and without discomfort after procaine infiltration. This treatment was extensively reported in the service journals during the recent war and was used to great advantage.

Successful as this treatment seems to be, there remain some undesirable features of the injection therapy. First, it involves the use of needles and sterile solutions and many patients rebel at the thought of injections into already painful areas. Second, routine infiltration into damaged tissues sooner or later results in contamination and a septic joint with its permanent changes in the articulating surfaces.

Ethyl chloride spray—The use of ethyl chloride spray to obtain relief of pain in ankle sprain has been used extensively by the author and his associates in treating this injury in army troops. The method employed is as follows:

After determining by physical and x-ray examination that the injury is not a malleolar fracture or a complete tear of a lateral ankle ligament, the patient is instructed to point out the painful areas around the ankle. These areas are then sprayed

with ethyl chloride until the skin is blanched and firm. Massage of the tissues is employed to relieve the transitory discomfort of the intensely cold spray. Thereupon the patient is told to stand with full weight on the injured ankle and if pain is still present in an area not treated, a second spraying is given. The patient is encouraged to walk with full weight on the injured ankle, not favoring it by limping. At this point the universal reaction is always intense surprise that walking does not cause pain. The ankle is then wrapped snugly with an elastic bandage and the patient is returned to duty, to work or his regular activity. He is instructed to wear the supporting bandage for 10 to 14 days and to return for treatment if pain develops in the ankle. Occasionally a second treatment is necessary 12 or 24 hours later, but this is the exception rather than the rule.

CONCLUSION

The rapid restoration to normal activity of the patient with an ankle sprain by this simple method of treatment has been most gratifying. Patients, who under old methods of treatment would be incapacitated for days to weeks, are almost immediately returned to normal activity. The widespread use of this method of treatment would greatly reduce the morbidity from this common injury.

REFERENCES

1. Wright, J. M., Parker, L. O., and Lehan, T. R.: Sprained ankles. U. S. Nav. M. Bull. 42:1819 (June) 1944.
2. Allen, J. H.: Trauma to the foot and ankle. S. Clin. North America 27:1506 (December) 1947.
3. Leonard, M. H.: Injuries of the lateral ankle ligaments. J. Bone & Joint Surg. 31A:373 (April) 1949.
4. Gibney, V. P.: Sprained ankles. New York State M. J. 61:193, 1895.
5. Leriche, R.: Novocaine treatment of sprained ankles. Presse Med. 44:79 (January 15) 1936.
6. Leriche, R., and Arnulf, G.: Novocaine treatment of sprained ankles. Am. J. Surg. 32:45, 1936.
7. Bakst, H. J., and McCormick, G. W.: Use of local anesthesia in treatment of contusions and sprains. U. S. Nav. M. Bull. 41:107 (January) 1943.
8. Webber, J. T.: Ambulatory treatment for sprained ankle. West Virginia M. J. 40:176 (June) 1944.
9. McLaughlin, C. W., Jr.: Procaine infiltration in the treatment of acute sprains. Military Surgeon 97:457 (December) 1945.

Adequate Treatment for the Diabetic of Today

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What are the components of an adequate diet for the diabetic patient? To say that we supply a certain number of calories per day for the diabetic is not enough. The diabetic cannot live by calories alone. If too large a proportion of the total calories is made up of fat, how is the patient going to replace the daily loss of sodium, potassium, calcium, chloride, iodine, iron, and all the other minerals, the water-soluble vitamins, and the ten essential amino acids, without which the human organism deteriorates and disintegrates?

In the general run of cases, 50 per cent of diabetics come to us at the ages of 40 to 55 years, of whom 85 per cent give a history of prediabetic obesity, weighing 50 to 150 pounds above normal. Ninety per cent of diabetics, at the time of their first visit, are still overweight; only 10 per cent are underweight. Most diabetics are overnourished and malnourished, and when they first come to us, their body chemistry and fluid exchange are seriously disturbed in many ways.

As a matter of principle in the treatment of all diseases, our constant aim and the best approach that we know is to strive for restoration or maintenance of a normal state of nutrition.

This brings up the question, "What is normal?" What is normal body weight, and what is a normal diet? In search of answers to these questions, fortunately for us, we are today coming into a better position than ever before.

Presented at the Postgraduate Assembly (Endocrinology-Diabetes), The Association for the Study of Internal Secretions and The American Diabetes Association, Miami Beach, Florida, April 7, 1950.

BODY WEIGHT

For the first time, we now have a more logical

TABLE 1

MAXIMUM LONGEVITY TABLES

IDEAL WEIGHTS FOR MEN—AGES 25 AND OVER

HEIGHT (WITH SHOES)		WEIGHT IN POUNDS (AS ORDINARILY DRESSED)		
		SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Feet	*Inches*			
5	2	116-125	124-133	131-142
5	3	119-128	127-136	133-144
5	4	122-132	130-140	137-149
5	5	126-136	134-144	141-153
5	6	129-139	137-147	145-157
5	7	133-143	141-151	149-162
5	8	136-147	145-156	153-166
5	9	140-151	149-160	157-170
5	10	144-155	153-164	161-175
5	11	148-159	157-168	165-180
6	0	152-164	161-173	169-185
6	1	157-169	166-178	174-190
6	2	163-175	171-184	179-196
6	3	168-180	176-189	184-202

TABLE 2

IDEAL WEIGHTS FOR WOMEN—AGES 25 AND OVER

HEIGHT (WITH SHOES)		WEIGHT IN POUNDS (AS ORDINARILY DRESSED)		
		SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Feet	*Inches*			
4	11	104-111	110-118	117-127
5	0	105-113	112-120	119-129
5	1	107-115	114-122	121-131
5	2	110-118	117-125	124-135
5	3	113-121	120-128	127-138
5	4	116-125	124-132	131-142
5	5	119-128	127-135	133-145
5	6	123-132	130-140	138-150
5	7	126-136	134-144	142-154
5	8	129-139	137-147	145-158
5	9	133-143	141-151	149-162
5	10	136-147	145-155	152-166
5	11	139-150	148-158	155-169
6	0	141-153	151-163	160-174

(Metropolitan Life Insurance Co.)

approach in the use of the so-called Maximum Longevity Tables, based on studies of somewhere near a million men and an equal number of women and prepared by the Metropolitan Life Insurance Company (Tables 1 and 2). We adopted the Maximum Longevity Tables in our work when they were first reported, about seven years ago, and up to this time have found no reason to question their validity or usefulness. A valuable feature included in these tables is the fact that they account for normal variations in size, allowing more for persons of medium and large frame than for those of small frame, at the same body height. Out of these tables, we select an ideal or a desired weight for the diabetic patient.

CALORIC REQUIREMENT

Our next step is to decide on caloric requirement for the patient. Here again we are guided by normal values. We allow 25 calories for every kilogram (2.2 pounds) of body weight for a patient in bed, or for an elderly man or woman, one who lives a sedate and quiet life. We allow 27.5 calories per kilogram of body weight for a patient who should be on a moderately low diet—a patient of middle or past middle age. For the obese patient whom we wish to reduce, we allow 25 calories per kilogram, and at times less than that. For the physically active or for growing young people, we allow 30 calories per kilogram. We believe that the diabetic should, at all times, avoid luxus diets—diets containing more nutriment than is really necessary.

COMPONENTS OF THE DIABETIC DIET

What should go into the making up of a diet for the diabetic? In a large measure, we do know the purposes and the needs for carbohydrates, proteins, fats, minerals and vitamins. What we would like to know more about is exactly what proportion of each of these components makes up an ideal diet—one to keep the human metabolism working smoothly; one in which the building up and the breaking down of tissue would go on uninterrupted, without excesses and without deficiencies. We would particularly like to know the part played by fat in the diet. Is fat simply a storehouse for calories? Does fat represent a metabolic pool to which fragments are added and taken out, as they are needed? Until we have final answers to such questions, we must carry on with the knowledge we already possess. At present, we go on the assumption that two-thirds of the calories of a normal diet should come from carbohydrates, one-sixth from protein, and one-sixth from fat.

THE NUTRITIONAL STATE

I have already indicated how we meet the total requirement per day, based on body size, weight and physical activity of the patient. I would like to repeat and emphasize that, in our experience, the metabolism of the diabetic should not be overtaxed at any time, and that the diabetic should be maintained on a conservative basis from the standpoint of nutrition. We know that the majority of diabetics do well on considerably less than 2,400 calories per day. On reviewing a series of 100 adult patients under good diabetic control, I found that the average caloric intake for the group, as near as we can estimate, was 1,700 calories per day. This was made up of carbohydrate 180 gm., protein 65 gm., and fat 80 gm. The average insulin requirement for this group was 36 units per day. I am convinced that the diabetic lives best, and avoids or delays complications, when he lives on a sustenance diet—one which maintains him in normal good health, without overeating. The diabetic

should take advantage of the natural laws of conservation in the metabolism.

The protein portion—No patient should be given less than 2/3 gm. of protein per kilogram of body weight. Less than that may lead to nitrogen loss. A good average protein allowance is 3/4 gm. per kilogram, and for the young and for meat eaters, as much as 1 gm. per kilogram of body weight. Hypoproteinemia—secondary anemia—and other disturbances may come with insufficient protein, and this should be avoided. In our experience, women find that 1 gm. of protein per kilogram supplies more meat or meat foods than they desire, and 3/4 gm. of protein per kilogram is altogether satisfying.

The fat portion—There is no scientific agreement today on the ideal or optimal fat portion in the diet. We know that a high fat diet is conducive to excess production of ketones and to the need of more rather than less insulin, to higher blood cholesterol, and to other less easily recognized secondary effects. In our experience, blood cholesterol is usually lowered after 10 to 14 days on maintenance diets. Having prescribed low fat diets for diabetics since 1923[1] we are convinced that the diet of the diabetic should be low in fats. We therefore plan our diets as low in fats as is consistent with a satisfactory menu for the day. Thus it was that we settled on 90 gm. of fat per day as supplying a satisfying diet for the diabetic.

Along with the low fat diet, for the past five years we have been recommending, as much as is practical, the use of vegetable fats and oils in preference to animal fats, with their higher cholesterol content, for the diabetic patient.[2] What we are aiming at is to reduce the tendency to ketosis and to delay or avert the ever present likelihood of arteriosclerosis, if that is possible, by means of diet. This position is being substantiated by the studies of Houssay,[3] Martinez,[4] and others, on the effects of animal fat and high fat diets in the production of experimental diabetes. Research that is being carried on today by Gofman and his associates in the Donner Laboratory at the University of California, suggesting that there are certain lipids and lipoproteins that play a role in the cause of atherosclerosis, may prove to be of real significance.[5,6]

The total diet—Whatever the formula for the individual diabetic, we make certain that the daily diet obtains more calories from the carbohydrate and protein portions than it does from the fats. To meet the total caloric requirement for a day, we calculate the caloric value of the proteins and fats already prescribed, and make up the balance in carbohydrates.

FORMULA FOR THE DIABETIC DIET—ADULT

Protein 0.66 or 0.75 or 1.0 gm. per kilogram of body weight
Fat approximately 90.0 gm. per day
Carbohydrate q.s. for total caloric need per day

ORDERING THE DIET

Patient's weight 143 pounds = 65 kilograms
At 30 calories per kilogram: 30 x 65 kilograms = 1,950 calories per day
Protein 1.0 gm. x 65 kilograms = 65 gm. protein per day
Fat 90 gm. per day

CALCULATION

Protein 65 gm. x 4 calories = 260 calories
Fat 90 gm. x 9 calories = 810 calories
Protein and fat supply 1,070 calories
1,950 calories = total daily requirement
1,070 calories = supplied by protein and fat
880 calories to be supplied by carbohydrates
880 calories 4 calories per gram = 220 gm.
Daily diet therefore is: Carbohydrates 220 gm., protein 65 gm., fat 90 gm.

INSULIN

If, on an adequate maintenance diet, the patient becomes sugar normal, then he is continued on that diet and does not require insulin. In our experience that applies to at least 40 per cent of diabetics. On the other hand, if the patient continues to excrete sugar, after several days on this diet, insulin is necessary. The question then is how much insulin? And the answer to that is simple—enough insulin to cause disappearance of urine sugar and a nearly normal blood sugar level (120 mg.).

As we see it now, not to give enough insulin is to fall short of complete treatment of the diabetic. To give too much insulin may be to initiate a series of disturbances that will be upsetting in ways that are undesirable, unnecessary, and altogether avoidable. Excessive doses of insulin call forth reactions which in turn may even lead to hyperglycemia. It is well known that prolonged hyperglycemia leads to loss of carbohydrate tolerance in animal and man. Excess insulin inhibits the islands of Langerhans or their beta cells, and when the insulin is stopped, temporary insufficiency follows.[7] All this naturally comes into our calculations in our approach to the treatment of the new diabetic.

Manifestations of excess insulin—At this point, I wish to emphasize two types of disturbance which occur when the patient receives more insulin than is necessary. The first may occur shortly after beginning treatment of a new diabetic, as well as any time thereafter. The patient who comes to us "loaded" with sugar, so to speak, having high glycosuria and hyperglycemia, will for the time being require a relatively larger dose of insulin, at least until he is made sugar free. At that time, in the interest of early control, there is reason enough for giving liberal doses of insulin until the patient

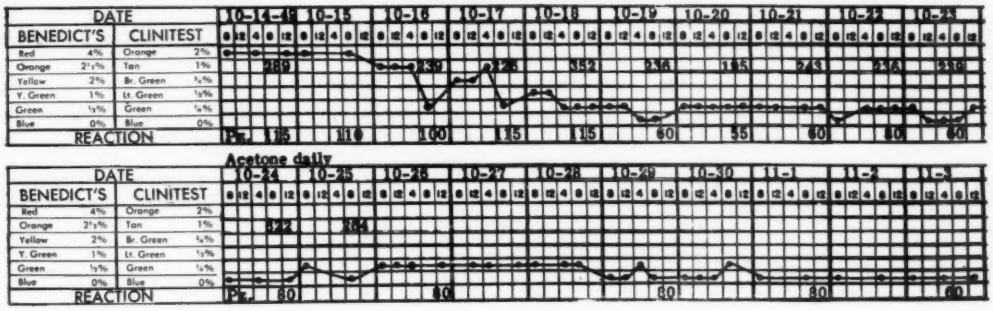

FIGURE 1

becomes sugar free. If, however, the amount of insulin per day is in excess of what he really needs, he will have insulin reactions, and that calls for prompt reduction in dosage.

Excess insulin—There is a group of patients in whom insulin excess is not so apparent, and yet it is very real. This second group of patients may not have insulin reactions, but their blood sugars tend to be considerably below average normal values. They feel well and look well, except that they gain weight too rapidly. A critical examination shows that their tissues are overfull and tense and slightly waterlogged. They come in, having gained 10 to 20 pounds in the course of two to three months. Their friends tell them how well nourished they are, and they tell you how well they feel. In these cases, the question to my mind has been whether we should continue with that liberal dosage of insulin, or reduce it to the point at which blood sugar is maintained at a normal level, but not lower. One does not see any direct ill effects as a result of this moderate hypoglycemia and the patient's sense of well being is something that has its positive advantages.

On the whole, however, in most patients, we believe it is wise to lean to the side of conservatism and reduce the insulin dosage sufficiently to avoid excess gain in weight, which in a large measure is due to water retention. We all know that the patient who does not have enough insulin becomes dehydrated; this one, who gets more than enough insulin, becomes overhydrated.

Another type of disturbance which comes with excess insulin presents a more complex picture, and one less easily discerned. Every so often, we see patients who, having had severe glycosuria, had been given, in quick succession, large doses of insulin. This happens especially when patients are given insulin every four or six hours, according to the percentage of sugar in the last specimen voided. I have seen this occur in surgical cases, when the patient was given 5 or 10 units of insulin every four hours when the urine specimen is green, 10 to 15 units if the specimen is brown or yellow, and 20 units when the test shows red.

In principle, this entire procedure has an element of basic error, because a specimen of urine voided at 4 P.M., containing 3 per cent of sugar, may have been secreted into the bladder any time during the preceding four to six hours, and by the time the test is made, the patient's blood sugar may already have fallen off to a much lower level, and the insulin given after the positive test drives down an already low blood sugar to a still lower level. If this is allowed to go on, we have a zigzag type of urine sugar curve which resembles that of the so-called "brittle diabetic." I believe that some patients are made this way by repeated overdosage with insulin. What they need, and what stabilizes them after they are taken in hand, is more moderate doses of slower-acting insulins, and at times an adjustment in diet to avoid an excess food intake at one meal, and not enough at the others (Figure 1). And that is not all. These patients, given too large doses of insulin, have a rapid fall in blood sugar, and their livers are temporarily exhausted of available glucose and glycogen, after which excessive fat is burned to meet the immediate needs. All of this leads to overproduction of acetone which appears in the urine. In some of these patients, before they were brought to the hospital, when acetone was found in the urine, even larger doses of insulin had been given to overcome the ketosis; that only added insult to injury, with both doctor and patient in a state of distress.

This occurs more often than is generally realized; and if it were recognized by everyone who prescribes insulin, there would be fewer difficult cases to handle.

We would therefore say, that adequate dosage of insulin means just what is implied; not too little and not too much. In the light of daily experience, I am convinced that for an adult group of diabetics, certainly the kind of patients that we see, the average daily dose required will be somewhere near 35 units. Lowering that dosage causes a return of the diabetic state, and giving excessive doses leads to disturbances that can be avoided.

Type of insulin—In the treatment of a new dia-

betic, we are confronted with the problem of selecting the type of insulin best suited to the patient. Thus the question is, which insulin and how many units per day? During the past 27 years, we have run the gamut of searching for the most useful insulins. Our best answer to that is perhaps to be found in what we are doing now, in our everyday work. With that in mind, for the purpose of this discussion, I reviewed the last 100 cases in my service with the following findings.

The average size dose for the group as a whole was 37 units per day. In most cases, we use a combination of protamine zinc with regular insulin. We speak of the protamine zinc as the "night insulin" and the regular as the "day insulin." The protamine zinc insulin taken at 8 A.M. becomes quite effective in about eight hours, and its cumulative effect is active through the night. The regular insulin, which we speak of as the day insulin, becomes active within an hour or so after it is given, and continues for seven to eight hours. This being so, the regular insulin covers the breakfast to late afternoon period, following which time the protamine zinc carries through the rest of the day and night.

Because of the many variables within the patient himself, the patient's response is not always as prompt or as invariable as we would like, but it certainly is satisfactory in the majority of patients. It is important to realize that the apparent failure to control a diabetic may not be due to the insulin at all, but to other disturbing factors in the case.

In this group of 100 patients, all of whom were under good control when leaving the hospital and thereafter, 90 per cent were taking a mixture containing 1 to 1½ units of protamine zinc to 2 units of regular insulin. Since insulin mixtures have come into use, we have been using the so-called "made to order" combination, beginning with protamine zinc 1 to regular 2 units, and then adjusting the amounts of each to fit the individual needs during day and night. We use globin insulin in cases where the response to our usual procedure is not satisfactory.

It should always be remembered that "a unit of insulin is a unit of insulin" and the only difference in the effects of the various insulins is in the absorption rate and, therefore, in the sugar lowering effect. No doubt, in time to come, other preparations and other insulin mixtures may come into use; time will reveal their advantages and disadvantages. Our patients, once properly instructed, seem to have no difficulty in mixing and measuring the proper amounts of insulin in one syringe, for the single daily injection.

WHAT IS THE MEASURE OF GOOD CONTROL?

The ideal of satisfactory control is normal blood sugar and absence of urine sugar throughout the 24 hours. It is not enough to achieve successful control during hospitalization only; the sugar-free state should be maintained throughout the remainder of the patient's life. Everyone who treats diabetics knows that this ideal is not always attainable; nevertheless, that is our goal, and the nearer one comes to that ideal, the better for all concerned.

A survey of the records of 55 consecutive cases, in which their daily sugar tests had been recorded, showed that out of 17,687 tests, 74 per cent were sugar free, 11 per cent showed a slight trace only. This leaves 15 per cent of the tests showing a measurable amount of sugar. To that extent we may say that self care of the diabetic can be satisfactorily carried out. In a group of 50 patients, covering a period of one year, all kinds of upsets may occur, and an 88 per cent sugar free state may be considered quite satisfactory.

Expressed in simple terms, the diabetic is diabetic so long as he shows hyperglycemia and glycosuria. He is in a "nondiabetic" state when he is sugar free and has a normal blood sugar; and our aim is to keep him as "nondiabetic" as possible.

CONCLUSION

In concluding, I would say that diabetes, in our day, can be one of the most successfully treated of all diseases. Its treatment should be based on knowable facts gleaned in the fields of chemistry, nutrition, metabolism and clinical medicine. And by all that can be foreseen today, the future is bound to bring new enlightenment and in all likelihood, better treatment than we have ever had in the past.

REFERENCES

1. Barach, Joseph H.: Normal standards in treatment of 100 cases of diabetes with insulin. J.A.M.A. 32:247-251 (February 2) 1924.
2. Barach, Joseph H.: Arteriosclerosis and diabetes. Am. J. Med. 7:617 (November) 1949.
3. Houssay, B. A., and Martinez, D.: Experimental diabetes and diet. Science 105:584, 1947.
4. Martinez, D.: Influencia de la Dieta Sobre la Diabetes en la Rata. Rev. Soc. Argent. de Biol. 22:414, 1946.
5. Gofman, J., Lindgren, F., and Elliott, H.: Ultracentrifugal studies of lipoproteins of human serum. J. Biol. Chem. 179:973, 1949.
6. Gofman, J., Lindgren, F., Lyon, T., et al.: The role of lipids and lipoproteins in atherosclerosis. Science 111:166, 1950.
7. Ingle, D. J.: The Production of Experimental Glycosuria in the Rat. Recent Progress in Hormone Research, Vol. 2. New York, Academic Press, Inc., 1948.

EDITORIALS

Postgraduate Medicine FOR THE CONTINUING EDUCATION OF THE PRACTICING PHYSICIAN

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JANUARY 1951

PARKINSONISM

First described in classic terms by Sir James Parkinson, paralysis agitans is well recognized today in its clinical and pathologic aspects. It is customary to speak now of *Parkinsonism,* in tribute to its first describer, as a rather stereotyped syndrome characterized by two fundamental clinical features, a unique muscular rigidity and a rhythmic muscular tremor. These may be combined in varying proportions, and often are supplemented by aching pain, sialorrhea, and an oily, moist skin. The pathologic substratum is destruction of parts of the basal ganglia, particularly the caudate and lenticular nuclei and the substantia nigra.

Nosologically, Parkinsonism is subdivided into *paralysis agitans (Parkinson's disease)*—an affliction of age, due to primary, senile, degenerative changes—and symptomatic Parkinsonism, the result of chronic inflammatory, toxic, vascular degenerative, or even neoplastic processes. The clinical distinction between primary, degenerative paralysis agitans and the various symptomatic forms of Parkinsonism is sometimes easy but more often difficult, and, in view of the generally progressive course of almost all cases, such distinction is of little aid in therapy.

No known treatment affects the course of Parkinsonism except in rare instances in which removal of a tumor is said to have cured the condition. The hope of James Parkinson in 1817, "that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped," has not yet been realized, 133 years later. All therapy is symptomatic and meliorative. For many years nonspecific drugs were used, such as arsenic, strychnine, or opium, but for perhaps 100 years the alkaloids of the solanaceous (belladonna) group of plants have been the mainstay of the physician. Gowers credits Charcot with suggesting hyoscyamine, later largely replaced by hyoscine, as suggested by Babinski and many others. Stramonium and atropine were somewhat less effective. Many special combinations of these alkaloids have been promoted, such as Bulgarian belladonna, RABELLON, VINOBEL, etc.

Today it is the consensus of most physicians that hyoscine is by far the most effective drug for the relief of muscular rigidity, tremor and sialorrhea. However, in the aged, and in those peculiarly susceptible, hyoscine is apt to produce mental confusion, hallucinosis or nightmares. In such cases reliance must be put on stramonium, a combination such as rabellon, or some other preparation. In general, the barbiturates are contraindicated in Parkinsonism, since they tend to

exaggerate the rigidity and tremor. A valuable aid is amphetamine, administered morning and noon, which increases the patient's energy and enthusiasm for activity. It is best used in conjunction with hyoscine or stramonium.

New drugs, introduced under proprietary names have been suggested in recent years. Though vigorously defended, each has fallen short of the claims of its defenders. ARTANE (3[1-piperidyl], 1 phenyl, 1 cyclohexyl, 1 propanol hydrochloride) has been most prominently featured, while others are PANPARNIT (2 diethylaminoethyl, 1 phenyl, cyclopentane carboxylate hydrochloride) and DIPARCOL (diethyl-aminoethyl-N-thio diphenylamine hydrochloride). Like the belladonna group, these all dilate the pupils and dry the mouth, and, significantly, the beneficial effects of each seem roughly proportional to this atropine-like effect. Minor undesirable side-effects include gastric irritation, "nervousness," dizziness, and mental perturbation in varying degrees. MYANESIN (alpha, β-dihydroxy [2-methylphenoxyl] propane), with a mildly curare-like effect, has also been widely tried in Parkinsonism but without significant success.

The unfortunate Parkinsonian patient, living inseparably with his affliction, usually greets any new regimen with temporary enthusiasm. His emotional attitudes must not prejudice our objective appraisal. In the experience of the writer, none of these newer drugs is as effective as the belladonna alkaloids with adjuvant amphetamine. They are welcome as alternatives for the exceptional patient, as temporary substitutes, and as aids combined with the more effective drugs.

The tremor of Parkinsonism is abolished by hemiplegia; the same may be accomplished surgically by removal of the precentral gyrus (Bucy), by section of the anterior limb of the internal capsule (Meyers and Browder), by interruption of the lateral portion of the cerebral peduncle (Walker), or by cutting the lateral pyramidal tract in the spinal cord (Putnam). In all these instances, rigidity is not diminished, but rather increased, and paralysis of some degree is produced, which may lessen with time. Such surgical attacks are as yet in the investigative stage, and must, in any event, be reserved for very severe and, preferably, unilateral cases—a combination which is rarely encountered.

Thus, for all practical purposes, the treatment of Parkinsonism is medical, imperfect though it be. It is to be hoped that still other and newer substances will be tried and found helpful since a variety of remedies lends flexibility to our therapeutic efforts.

ROLAND P. MACKAY, M.D., *Department of Neurology and Neurologic Surgery, University of Illinois College of Medicine, and St. Luke's Hospital, Chicago.*

EXPANSION OF THE UNITED STATES PUBLIC HEALTH SERVICE

THE chief health agency of the United States is the United States Public Health Service. From the time when the United States Public Health Service was established as the Marine Hospital Service in 1798 to the present when its ramifications are concerned with practically every aspect of medical and public health services, its expansion has continued with increasing scope and intensity. At present the United States Public Health Service is seeking additional physicians to meet its expanded needs. For instance, it now wishes 15 qualified physicians to aid with the ECA program in the Far East, 3 physicians to serve in its mission in Liberia; indeed, more than 100 physicians are needed for foreign services in 1951.

Among the most significant of all of the activities of the United States Public Health Service however are its national advisory councils and its national institutes of health.

Outstanding dates in the growth of the United States Public Health Service are 1893 when quarantine became a full federal function; 1902 when the control of biologics was assigned to the service; 1930 when the Hygienic Laboratory was changed to the National Institute of Health; 1935

when grants to the individual states for health purposes were authorized under The Social Security Act; 1937 which saw the establishment of the National Cancer Institute; 1944 when research grants and fellowships were created for the Public Health Service; 1945 which saw the passing of the National Mental Health Act and the Hill-Burton Act for hospital survey and construction; 1947 when grants-in-aid to the states for cancer control were authorized and when funds were provided to begin the Clinical and Laboratory Research Center for the National Institute of Health; next came 1948 with the passing of the National Heart Act and the National Dental Research Act.

More recently the entire division has been reconstituted into bureaus with many divisions. The Bureau of Medical Services has eight divisions and the Bureau of State Services has fifteen. The National Institute of Health includes divisions for experimental biology, microbiology, cancer, heart, dental research, mental health and a division of research grants and fellowships. The budget of the United States Public Health Service has grown from less than one million dollars annually in 1800 to approximately 200 million dollars in 1950.

The publications of the United States Public Health Service are being reorganized and reconstituted since its various periodicals and other publications now make it among the leading medical publishing agencies of the world.

The professional staff of the national institutes of health include 675 scientists with 21 different specialties. The medical library includes more than 60,000 volumes. The Clinical Center now in process of construction is a 14 story building in Bethesda, Maryland which can care for 500 patients in connection with research on cancer, heart disease, metabolic diseases, mental and nervous diseases, infectious and tropical diseases and dental diseases. The annual report of the Federal Security Agency for 1949 covering the United States Public Health Service is replete with data concerning the scope of research in all these fields.

The medical profession has special interest in the research grants made by the United States Public Health Service which are reviewed by National Advisory Councils, two more of which were just authorized during the last session of Congress. Among these are the advisory councils on arthritis, on rheumatism and metabolic diseases, on cancer, on neurologic diseases and on blindness. In addition are the National Advisory Health Council, the National Advisory Mental Health Council, the National Advisory Heart Council and the National Advisory Dental Research Council. During 1949 these councils approved 1091 applications for almost 11 million dollars of Federal funds. The total grant programs now total about 50 million dollars a year. The councils meet one or two days quarterly to review applications for grants and make recommendations.

Most physicians who misguidedly depreciate every participation by government in medical education, research and medical care should devote the necessary time to a detailed study of the extent to which government, including federal, state, county and municipal, is now participating in just these activities. The recent report of the United States Public Health Service emphasizes that financial grants are undoubtedly the government's most effective method of helping state and local health work. In 1949 such grants expended more than 79 million dollars. Those who agitate for complete Federal control of medical care might well investigate the extent to which government already participates in medical care through its grants to the individual states which employ more than 20,000 people in carrying out expanded health programs including 2000 diagnostic and treatment clinics for venereal disease, 3500 child health centers, 375 pediatric clinics, 1500 maternity clinics, 1230 centers for tuberculosis and artificial pneumothorax, 60 diagnostic and treatment clinics for cancer, 130 mental hygiene clinics and 200 general clinics. All these clinical services depend for their effectiveness on

participation by local physicians. As to the future here is a quotation from the 1949 report:

"The Public Health Service is convinced that grants-in-aid will grow in volume and will supply an increasing proportion of the population with comprehensive health programs. In the past, grants-in-aid have blazed many new trails. Now they are beginning to merge in a single broad highway to better health."

In the United States medical care and care of the public health are undergoing a continuous evolution. Government has increasing participation with private agencies. Until now the right of patients to choose their physicians and the maintenance of mutual respect between doctor and patient have been maintained. The report of the Public Health Service for 1949 states as an ultimate objective the attainment of all of the goals set by the National Health Assembly of May, 1948. It envisions increasing expenditures for public health services and medical research with increasing participation by the social sciences. It proposes participation by government in the graduate education of physicians and the training of more health personnel. A final section of the report pleads for a cooperative effort in which commercial health insurance, voluntary prepayment plans and public medical care for special groups will work together in a comprehensive medical care program of high quality. Toward this end new research and new surveys are designed "to discover the best possible ways of financing, organizing and operating the services that we need for prompt care in sickness and for the promotion of health."

MORRIS FISHBEIN

DR. STURGIS IS IPMA PRESIDENT-ELECT

President-elect of the Interstate Postgraduate Medical Association for 1951 is Dr. Cyrus C. Sturgis, professor of medicine at the University of Michigan. The election took place at the 35th annual Assembly of the Association in Chicago.

Dr. Sturgis, who was born in 1891 in Pendleton, Oregon, obtained his B.S. degree at the University of Washington and his medical training at Johns Hopkins, receiving his M.D. there in 1917. He served in the Medical Corps of the U.S. Army during the first World War and later was a resident physician at Peter Bent Brigham Hospital in Boston.

From 1922-25, Dr. Sturgis was a teaching fellow in medicine at Harvard and was then appointed to an assistant professorship. He has been professor of medicine and director of the Thomas Henry Simpson Memorial Institute of Medical Research at the University of Michigan since 1927. Since 1928, he has been chairman of the department of internal medicine of University Hospital. Dr. Sturgis and Mrs. Sturgis, the former Una Smith, have three sons, Cyrus Cressey, Samuel Paine and William Smith.

The Medical Bookman

PRINCIPLES OF INTERNAL MEDICINE*

When I studied medicine in the period between 1908-1912 students were urged to inform themselves concerning the practice of medicine with the use of such books as Osler, Strümpell and the Anders textbook. The model of a textbook of the practice of medicine was the book by Prof. William Osler. This had already achieved the distinction of translations in French, Chinese, German and Spanish. The demand for the book was so great that Osler continued to make revisions through 1919. As he grew older, these revisions became a terrible trial. The Osler textbook of the practice of medicine put most of its emphasis on typhoid fever since that was at the time of its development the most important of the conditions usually seen by physicians. More recent textbooks begin with discussions of the common cold.

The time has now come when the possibility of a textbook on the practice of medicine written by one man is no longer conceivable. Even the Meakins has begun to include sections of considerable scope by other writers. The book by Cecil is the work of many authors. Up to the work by Harrison and his associates such textbooks have continued to follow the form so well established by Osler. Now, however, a new approach is followed.

Some of the factors in this work are distinctive. The volume begins with a section entitled "Approach to the Patient." Then come sections devoted to pain, weakness, shortness of breath and cough, disturbances in circulation and similar cardinal manifestations of disease. The second part of the book includes physiologic considerations such as inheritance, aging, fluid and electrolyte balance and normal emotional development. The third part involves reactions to stress and to antigenic substances with a new approach to allergic disorders and collagen disorders arising from stress according to this concept. The fourth part takes up the metabolic and endocrine disorders, including nutritional and hormonal disturbances. Part five comprises disorders due to chemical and physical agents. Part six concerns diseases due to biologic agents; in this section are discussed diseases caused by bacteria, viruses, protozoan organisms, worms and other living agents. Part seven takes up diseases of organ systems, including the blood, the cardiovascular system, respiratory, alimentary, digestive and nervous systems.

Another important factor in the development of this book is the youth of those who have participated. Hardly any of the contributors is over 50 years of age and the majority are under 45. In the preparation of this book the cooperation between the editors and the contributors has been exceptionally close. Multiple critics of varying background and experience have been given opportunity to see each of the chapters before it has been considered finally acceptable. Indeed even students of the type who would ultimately be expected to use the book in the study of the practice of medicine were given opportunity to express their opinions as to the clarity and adequacy of the preparation. Every chapter has, therefore, been revised at least once, some several times. Moreover, the chapters as finally considered suitable have then had the ultimate attention of editors and persons trained in typographical aspects of presentation. The book is, therefore, designed specifically for students and physicians with the understanding that what they require is thorough familiarity with common disorders and an understanding of the basic principles underlying disease.

As might be expected, this technic of presentation makes somewhat for unevenness. Many users of the book will feel that some special subject in which they are interested has been inadequately covered; yet they will find even for these areas of information up-to-date, carefully selected bibliographies pointing toward more comprehensive information.

An index, closely set with three columns to each large page and covering in all 45 pages, makes access to any specific bit of information easy.

*Principles of Internal Medicine, edited by Tinsley R. Harrison, M.D., Medical College of Alabama, Birmingham, with 53 contributors. 1,590 pages with 245 illustrations. 1950, The Blakiston Company, Philadelphia. $12.00.

POSTURAL INSTRUCTIONS

FIGURE 15. Postural instruction sheet, furnished to each patient following a thorough instructional course.

Exercises should be taken on a padded floor.

Exercise 4 should be omitted unless otherwise instructed.

Start exercises by doing each one_____times morning and evening, increasing the series one a day until you are doing each one_____times morning and evening.

Exercises are essential in obtaining a proper muscular balance but a correct posture is acquired only through conscious effort.

Remember—

1. When standing or walking, toe straight ahead and take most of your weight on heels.
2. Try to form a crease across the upper abdomen by holding the chest up and forward and elevating the front of the pelvis.
3. Avoid high heels as much as possible.
4. Sit with the buttocks "tucked under" so that the hollow in the low back is eradicated.
5. When possible, elevate the knees higher than the hips while sitting. This is especially important when driving (driver's seat forward) or riding as a passenger in an automobile.
6. Sleep on your back with knees propped up or on your side with one or both knees drawn up. Bed should be firm.
7. Do not lift loads in front of you above the waist line.
8. Never bend backwards.
9. Do not bend forward with knees straight. Always "squat."
10. Avoid standing as much as possible.

LEARN TO LIVE 24 HOURS A DAY WITHOUT A HOLLOW IN THE LOWER PART OF YOUR BACK

Here is a textbook of the practice of medicine which offers for the first time a really adequate presentation of the new concept of stress in relationship to a wide variety of disorders, an understanding of disease based on chemical and physical changes constantly going on in the human body and underlying a wide variety of disturbed conditions. Here, moreover, is a work arranged specifically for the teaching of medical students who approach the subject of internal medicine along the lines here comprehended.

Typographically the book is a work of art, printed with easily read two columns for each page, illustrated with diagrams and half-tones and sufficient colored pictures to enhance the text, supplemented with numerous tabulations for learning.

The young authors are among the leaders in the fields of investigation of the conditions which they discuss and the book is by this very reason a stimulus to further research. The wide acceptance of this textbook—more than 20 medical colleges within the first few months after its appearance—is an indication of the extent to which it meets the needs. Medical students and physicians in practice will find it a most useful book for ready reference.

M. F.

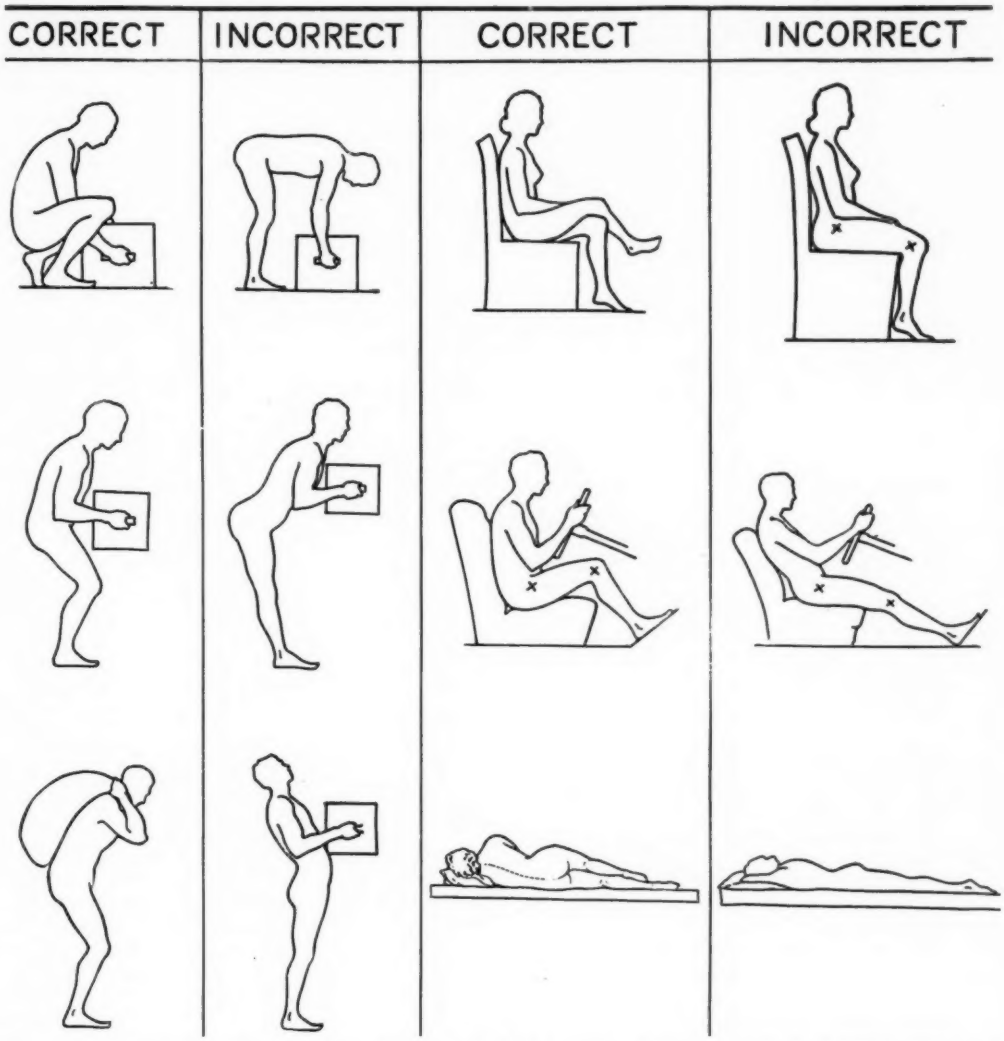


FIGURE 16. Reverse side of postural instruction sheet, showing correct and incorrect methods of lifting, sitting, and sleeping.

(Illustrations from "Principles of Internal Medicine")

► CEREBRAL PALSY - - -

By John F. Pohl, M.D., Orthopedic Surgeon, Michael Dowling School for Crippled Children, Minneapolis, Minnesota. 224 pages, with 131 illustrations. 1950, Bruce Publishing Company, St. Paul, Minnesota. $5.00.

Stressing the necessity of early diagnosis and treatment to achieve maximum results, the author has advanced an impressive volume on the problems of cerebral palsy. Objective findings which afford evidence of motor impairment are often late in appearance, and early symptoms must be recognized to institute immediate direction of the developmental patterns. To distinguish pathogno-

monic from assident symptoms is indeed a most difficult task as the neurologic responses which usually give sound support to the clinical impression are far too unreliable in the infant. This monograph tends to list findings suggestive of cerebral injury that will acquaint physicians with primary characteristics of the disorder.

The clinical varieties of cerebral palsy are listed with their rate of occurrence. Treatment is based on principles of muscular relaxation, voluntary muscle control and the establishment of developmental patterns which assist the extremity or portion involved to realize its ultimate function. The relaxation of involved muscles and neuromuscular training to institute muscle consciousness, secure muscle function and insure coordination are detailed in a clear, concise manner with individual muscle groups utilized for particular movements. This training is then directed so that progressive advancements toward the more complex activities can be performed without apprehension. Succeeding chapters on occupational therapy, walking and speech training which represent the ultimate goals in this type of rehabilitation are very instructive.

When one is aware of the tremendous number of victims of cerebral palsy and the estimated occurrence of ten thousand new cases each year, this accumulation of data resulting from a twelve-year comprehensive study becomes a must in the library of anyone interested in the problem. It is especially recommended for physicians whose specialties are closely related to the problem, and for physiotherapists whose knowledge and untiring efforts afford the most satisfactory results.

H. O'P.

► TEXTBOOK OF X-RAY DIAGNOSIS - - -

Edited by S. Cochrane Shanks, M.D., Director, X-ray Diagnostic Department, University College, London, and Peter Kerley, M.D., Director, X-ray Department, Westminister Hospital, London, with British contributors. Vol. III, Abdomen. 830 pages, 694 illustrations. Ed. 2. 1950, W. B. Saunders Company, Philadelphia & London. $18.00.

As one of four volumes of the complete textbook, this book includes the radiographic diagnosis of disorders of the alimentary tract, the biliary tract, the liver, spleen, pancreas, the urinary tract, and obstetric and gynecologic conditions. The other volumes in the set cover the central nervous system and head, the cardiovascular and respiratory systems, and bones, joints and soft tissues.

The technic of making films is not given, nor is the electrophysical basis of radiology explained, but methods of examination of the several fields are adequately described.

Notable are the section on the alimentary tract of infants and children; studies of the antenatal fetus and female pelvic measuration and fetal-pelvic proportion; discussion of obstetric prognosis and progress of labor as derived from radiographic evidence; and interpretation of the unusual appearance of the stomach and contiguous structures after gastric surgery.

The text is clear, concise and well organized. Surprisingly few concessions are required to British terminology or opinion. The illustrative films, apparently all original publications, are excellently reproduced on heavy enamel stock.

J. B. C.

► DISORDERS OF THE BLOOD - - -

By Sir Lionel E. H. Whitby, M.D.. F.R.C.P., D.P.H., University of Cambridge; and C. J. C. Britton, M.D., D.P.H., Bland Sutton Institute of Pathology, The Middlesex Hospital, London. Ed. 6. 759 pages, with 94 illustrations and 12 color plates. 1950, The Blakiston Company, Philadelphia & Toronto. $8.00.

Beginning with the origin, development, function and fate of the blood cellular elements, a complete hematologic study is herein presented from the point of view of histopathology, laboratory technic, clinical medicine and therapeutics.

The text begins with the origin, development, function and fate of the blood cellular elements. Then abnormal hemopoiesis is discussed. Three chapters are devoted to the principles and practice of hematologic diagnosis. The next 11 chapters thoroughly cover the anemias from every possible cause group and category. Separate chapters and summaries are written for megaloblastic, hemolytic, hypochromic, pregnancy, hemorrhagic, aplastic and the miscellaneous anemias.

Following a comprehensive coverage of anemias, the authors proceed to the polycythemias, leukemias and then the miscellaneous disorders associ-

ated with splenomegaly. One very interesting chapter is devoted to the infectious diseases with their clinical and hematologic aspects. Blood transfusions, hemagglutination and blood groups are discussed including the Rhesus factor and other intra-group agglutinins. Finally, the disorders involving the blood pigments are presented, including enterogenous cyanosis, porphyria and porphyrinuria. The last 100 pages are devoted to laboratory technic from the simplest of blood tests to the performance of the prothrombin, urobilinogen, porphyrin, bone marrow technics and the like.

R. W.

► PATHOLOGIC PHYSIOLOGY: Mechanisms of Disease - - -

Edited by William A. Sodeman, M.D. Contributors: Harry L. Alexander, William B. Bean, William B. Castle, Robert A. Cooke, Arthur C. Corcoran, Charles A. Doan, Robert Elman, John H. Foulger, Richard H. Freyberg, George T. Harrell, Jr., Edgar Hull, Franz J. Ingelfinger, Franklin D. Johnston, Joseph B. Kirsner, John S. LaDue, Irvine H. Page, Walter L. Palmer, Roscoe L. Pullen, Edward C. Reifenstein, Jr., Joseph T. Roberts, Robert F. Rushmer, Leon Schiff, John H. Seabury, William B. Sherman, William A. Sodeman. 808 pages, with 146 illustrations. 1950, W. B. Saunders Co., Philadelphia. $11.50.

What subjective symptoms and objective signs are to be expected from disease of a particular organ or system, and why and how they are evolved, are explained by the 24 authorities collaborating with Sodeman. The editor has chosen clinical investigators with teaching experience to resolve these questions.

The structure and morphology, blood supply and innervation of an organ are described on the framework for exposition of the normal physiology. Then the consequences of disordered function are examined and the perceptible and discernible manifestations of the derangements are described and explained. In the same manner, the foundation is laid for reasonable therapeutic management; for instance, the dynamics of the circulation upon which to balance physical activity and rest, water and salt intake and induced diuresis, medication with cardiac glycosides and control of peripheral and pulmonary circulation for a patient with heart failure.

Diagnosis should not depend upon empirical and descriptive data; therefore sufficient information is supplied for accurate interpretation of diagnostic procedures, for example, the electrophysical basis for electrocardiography.

Most of the charts and diagrams are new and obviously designed expressly for the relevant text. Information on any point is readily available by use of the adequate index, without the inconvenience of searching for cross-references.

J. B. C.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

Worth and Chavasse's Squint—Or the Binocular Reflexes and the Treatment of Strabismus. By T. Keith Lyle, M.D., M.R.C.P., F.R.C.S., Surgeon and Medical Officer in Charge, Orthoptic Department, Westminster Branch of the Moorfields, Westminster, and Central Eye Hospitals; Ophthalmic Surgeon, King's College Hospital and the National Hospital for Nervous Diseases, London; Civilian Consultant in Ophthalmology to the Royal Air Force. Ed. 8. 310 pages, with 208 illustrations. 1950, The Blakiston Company, Philadelphia & Toronto. $8.00.

1950 Year Book of Obstetrics and Gynecology. Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Gynecology, Cook County Graduate School of Medicine; Attending Gynecologist, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital; Associate Staff, Chicago Lying-In Hospital, Chicago, Illinois. 570 pages, illustrated. 1950, The Year Book Publishers, Inc., Chicago. $5.00.

Speaking of Man. By Abraham Myerson, M.D. 279 pages. 1950, Alfred A. Knopf, New York. $3.00.

The Neurologic Examination; Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. By Russell N. DeJong, M.D., Professor of Neurology and Chairman of the Department of Neurology, University of Michigan Medical School. 1,079 pages, with 368 illustrations. 1950, Paul B. Hoeber, Inc., New York. $15.00.

Advances in Internal Medicine. Editors: William Dock, M.D., Long Island College of Medicine, Brooklyn, and I. Snapper, M.D., The Mount Sinai Hospital, New York. Associate Editors: Tinsley R. Harrison, M.D., Chester S. Keefer, M.D., Warfield T. Longcope, M.D., and J. Murray Steele, M.D. 14 contributors. Vol. 4. 549 pages, illustrated. 1950, Year Book Publishers, Inc., Chicago. $10.00.

German-English Medical Dictionary. By Joseph R. Waller, M.D., and Moritz Kaatz, M.D. 224 pages, pocket-size. 1950, The Blakiston Company, Philadelphia & Toronto. $2.50.

When Minds Go Wrong. By John Maurice Grimes, M.D. 237 pages, illustrations by K. Alexandra White. 1950, published by the author, 5209 S. Harper Ave., Chicago 15, Ill. $5.00.

Men of Medicine

The Reluctant Surgeon

RIPE, now, in years and wisdom, Dr. Vilray Papin Blair sits often, looking from the windows of his sitting room, across the wide Missouri. Gone are the days when he rushed about St. Louis, driving with famous abandon a pink Pierce Arrow that was almost devoid of paint. As he drove he nibbled hastily at a cold fried egg sandwich and gulped from a bottle of milk. He would spend long hours cutting and arranging intricate paper patterns of the skin flaps to be grafted in rebuilding a mutilated face, but his meals and sleep he took in snatches.

The home in which he sits is an old farmhouse he bought and remodeled, as before it he had redone to high development a place in Fish Creek, Wisconsin. A friend, thinking also of a boat and a bus which had their faces lifted, has called him a bildomaniac. Like many creative people, when a project reaches completion, he loses interest. His pleasure is in the making, not the enjoying.

The present house is situated on a steep bluff, on land which might well have belonged to his family in earlier times, for it was one of his maternal ancestors, Pierre Laclede Liguest, who selected the confluence of the two great rivers as the site for his fur post, St. Louis.

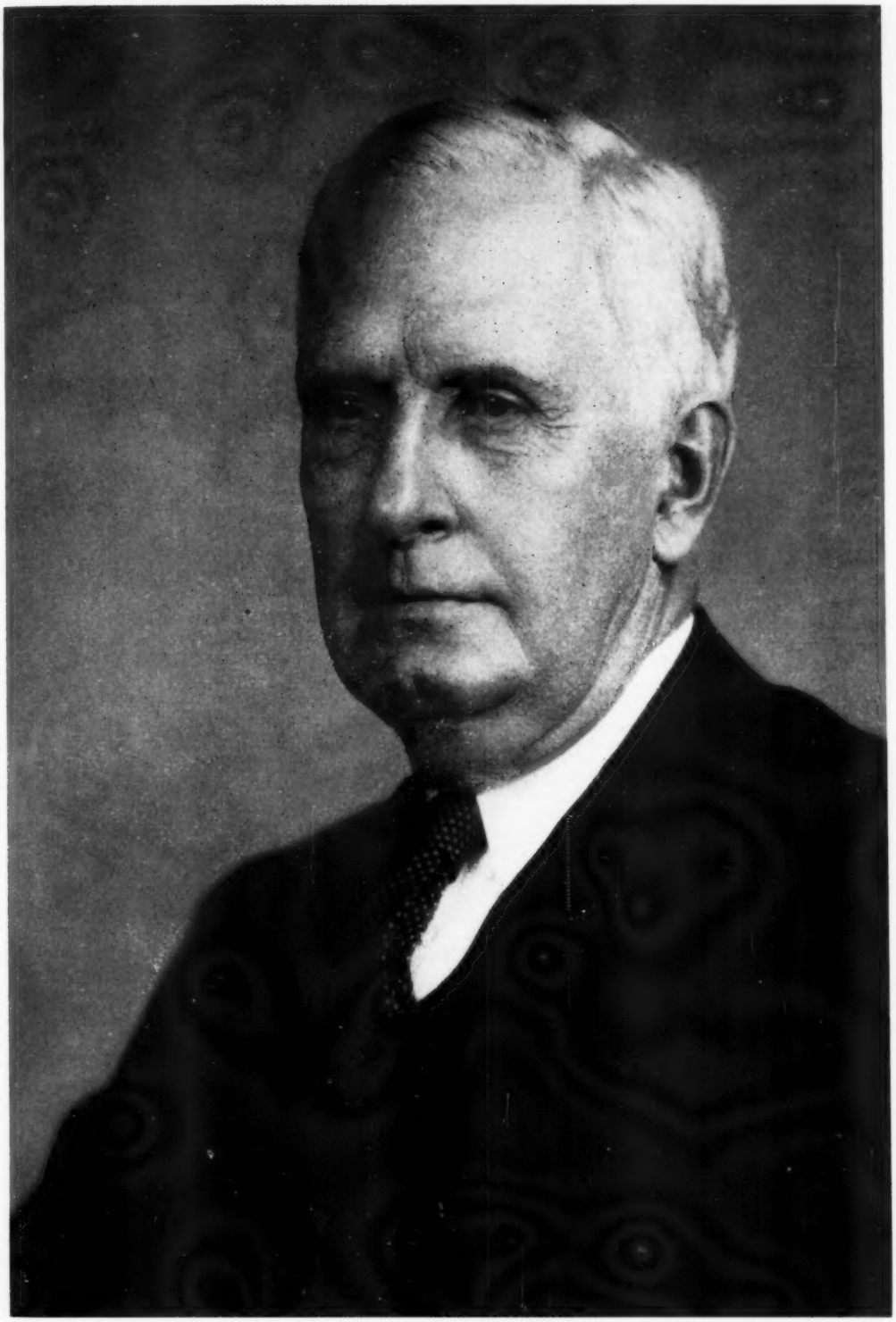
As the history of his family spans the history of St. Louis, so Dr. Blair's many years of practice cover much of the history of modern medicine. To it he has contributed many brilliant chapters. The most outstanding in the opinion of other plastic surgeons was the work which resulted in three pamphlets: The Influence of Mechanical Pressure in Wound Healing, The Delayed Transfer of Long Pedicle Flaps in Plastic Surgery, and The Use and Uses of Large Split Skin Grafts of Intermediate Thickness.

Dr. Blair's family tree bears on its branches many of the French names prominent in the city's history. For much of his childhood, he and his mother and sisters lived in the home of his grandfather, Dr. Timothy Loisel Papin. The old man was an extremely dignified Frenchman who insisted on being addressed as Doctor, even by his intimates.

The title was well deserved for he was a distinguished physician. After his graduation from St. Louis Medical School in 1846 Dr. Papin went to Paris to study. While he was there Sir James Simpson came to Paris to show the use of chloroform as an anesthesia. He asked for an interpreter and Dr. Papin was called upon. Sir James then let Dr. Papin give the anesthesia under his guidance so that Dr. Papin could say he was the first man to give chloroform upon the continent of Europe.

On his return to St. Louis, Dr. Papin brought the French knowledge of the use of the obstetric forceps, and early attracted much attention and some criticism. He wrote very few papers, contrary to the habits of his grandson, who has written over one hundred and fifty. Dr. Blair says, "When I worked on something and learned about it, I wrote about it." One paper Dr. Papin did write was a report on a long series of placenta previa cases with a remarkably low death rate. Back in the eighties Dr. Papin was already using rubber gloves when attending infected cases of parturition to, as he expressed it, "prevent carrying the disease to other women."

The family influence was strong on young Vilray to follow in his grandfather's footsteps. He, himself, claims that he was never a good student, and that he was a slow and inept reader. An associate who worked with him in the years of his great and brilliant activity, agrees that he was not a reader, making the laughing exception of detective stories. "He had a mind that worked so fast that none of us could keep up with him, but he didn't read. If he had an operation to do he thought about it and worked it out in great detail, planning every step. But he never went back to see if someone else had done it and how. His is a com-



VILRAY PAPIN BLAIR

pletely original mind. He figures out his approach and carries it out himself."

For a man who does not read Dr. Blair has a fine English style and knowledge of literature. He lays credit for that and for his retentive memory to his mother's constant reading aloud to the family circle from a wide range of French and English books. But favorite family stories bear out his contention that he was no scholar. They tell how he played hookey from school, especially in the fall when he would ride horseback out into the country to see the flocks of wild ducks that still flew in great numbers down along the Mississippi waterways.

With all his dilatoriness he graduated from Christian Brother's College in 1890 with a Bachelor's degree, and matriculated at the old St. Louis Medical College, which the year of his graduation became Washington University School of Medicine. At that time, Dr. Blair remembers, all subjects in the Medical School, even anatomy, were presented by formal lectures, "a few excellent, one classical, and some very uninteresting. I 'ditched' the latter along with the specialties, but I had a grounding in medicine and surgery, and got by in anatomy with a Gray, my only medical textbook."

The memory training he had received from his mother's reading must have stood him in good stead. for in addition to "ditching" the uninteresting courses, he "ditched" his entire second year. This he spent stringing telephone wires for a high potential experimental hydro-electrical installation in the Colorado Rockies. When he returned from that trip he wanted to give up medicine entirely and go to the Westinghouse Electrical Engineering School, but family pressure was too strong and he went back to medicine, graduating with his class. One wonders what a modern medical student, sweating through pre-med and the grueling years of medical training, would think of getting through in three years, one of them in absentia.

Talking of it, Dr. Blair, who shares the probable amazement of the modern student, says, "In addition to the dissecting room anatomy, there was one accidental circumstance that made the whole thing possible. Dr. E. H. Gregory, Professor of Surgery, was a brilliant lecturer and a conversational teacher. He was gifted with a grasp of surgical pathology that sent out tentacles constantly reaching for as yet undemonstrated facts, so that his teaching often antedated his time."

Even today Dr. Blair's face lights up as he speaks of his teacher and he says with enthusiasm, "That was the man!" But his debt to Dr. Gregory he has repaid in kind for he, too, has been a great teacher.

Through family connections young Blair formed the habit of dropping in at Dr. Gregory's late in the afternoon so that "with his teachings, the anatomy, and a lot of luck, I got my diploma."

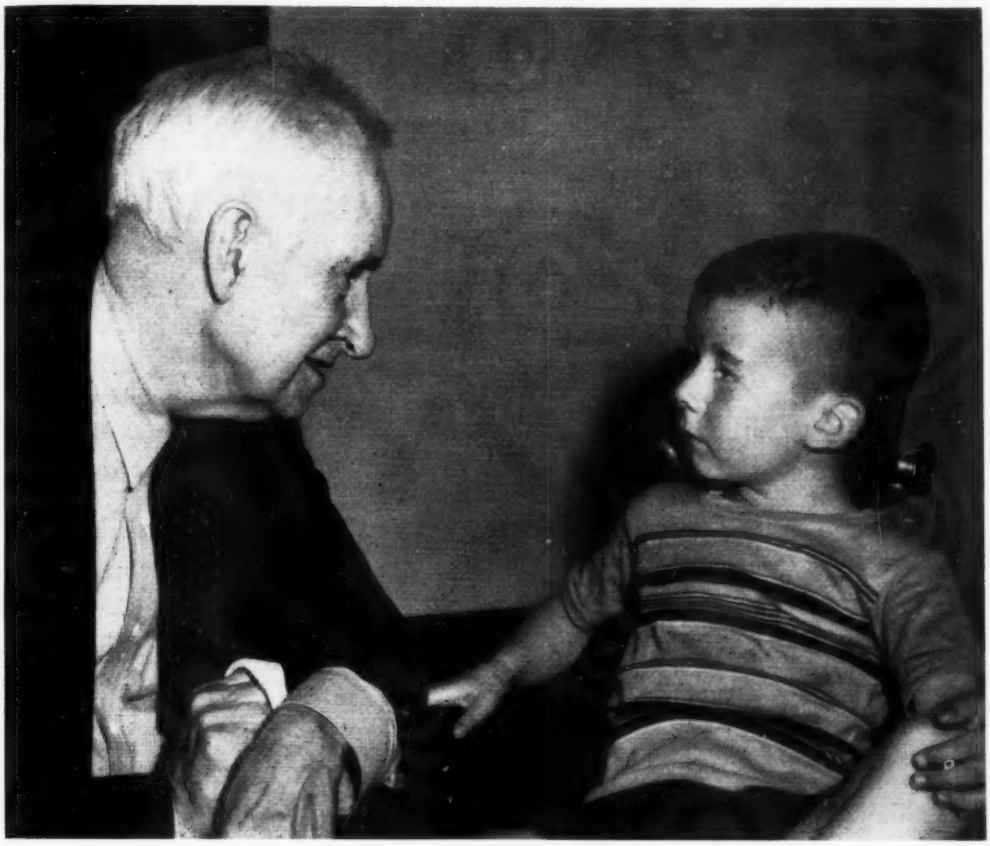
After graduation he applied for a position as assistant to Dr. Tupper, "one of the finest gentlemen ever born, and to whom I am sure I was a great trial. I never kept formal office hours but would show up for the hospital work, spending the rest of the time between Dr. Gregory's house and the Medical School!" He managed, somehow, on the side to take a Master's Degree from his old college, Christian Brother's. Those who now decry the single mindedness of medical training might do well to cite as a point in instance of their advocacy of other subjects the career of Dr. Blair.

"St. Louis surgery at that time," Dr. Blair relates, "was a bit primitive. Anesthesia and practical antisepsis had thrown wide the gates of surgery but it was of limited scope. Henry Mudd, who was far seeing and an organizer, was head of the Medical School. I was teaching anatomy, and conscious of my ignorance, always tried to follow to the letter the plans for the dissecting." Ignorant though Dr. Blair claims he was, the originality and flair for method that were to mark his whole surgical lifetime, came to the fore. Dr. Barney Brooks of Vanderbilt University who spoke before the St. Louis Medical Society meeting of May 20, 1947, which honored Dr. Blair with a certificate and medal of merit, told of conducting a laboratory in Surgical Pathology at the medical school at this time. He went into one of the classrooms and saw a great mass of modeling clay. Curious, he was told that this was the room in which Dr. Blair taught anatomy. Dr. Blair published a "Textbook for the Modeling of Human Bones in Clay" in 1906 and the method has since been widely used. Asked about this idea, Dr. Blair, with the characteristic modesty that causes him to refer to his accomplishments in surgery as "plumbing," shrugs and says, "It seemed the easiest way to teach."

"At that time," Dr. Blair continued, "some of the out of the ordinary cases were referred to me, and I tried to work out plans for operating, usually checking with Dr. Gregory. Those included brain tumors, attempts at establishing return circulation in liver cirrhosis, repair of harelip on day-old infants, infantile transplantation of ureter for bladder exstrophy, and trifacial neuralgia."

EVERYONE in his family has a different explanation for how Dr. Blair happened to pick the then very unusual field of plastic surgery. His youngest son's explanation is borne out by the list above. "Doctors who didn't want to risk their established reputations by doing bizarre operations referred them to Dad," John Blair says with a happy disregard for the reputations of unnamed doctors, long dead.

The operations proved too much for Dr. Blair. "The thing wasn't right. I lacked real surgical



A young patient talks things over with Dr. Blair.

training and though I lasted about six years the worries of it put me out."

Run down, mentally and physically, Dr. Blair went abroad. Had he followed his own instincts, he is apt to tell, he would have been a tramp all his life. Certainly, now that he is "forgetting medicine," it is the tramp interludes on which he likes to dwell. After traveling in Italy and France, he went to Edinburgh, meaning to go to the University, but found himself not up to it. He then had a series of his most interesting experiences.

The Boer War was on and English ships were short of surgeons. Dr. Blair had a stormy interview with the Port Doctor who refused to hire him because he did not have his medical credentials. He pawned a family watch for money to get back to Edinburgh, but on his return, received a wire from the Port Doctor, offering him a berth on the Dominic, bound for Para. He looked up Para in the atlas and accepted. On the trip he saw many European ports while cargo was taken on, and, after arrival, traveled a thousand miles of the Amazon and Negro Rivers. The ship returned to Liverpool with beriberi, yellow fever, and smallpox on board. Dr. Blair remembers an island burial and an over-the-side funeral every other day between Para and Madeira.

On one of the later trips he went to the coast of West Africa and up the oil rivers. One night on their trip down one of the group, a half-Negro explorer who was recognized by the Royal Geographic Society of London, took some of the ship's company to a "Father" making palaver in the huts of one of the chiefs. They sat about a table spread with a red cotton cloth under a magnificent crystal chandelier, eight feet around. At one end of the hut, before a woven silver cloth, a Negro, attired in a silk hat and little else, "was reaching the Father." The chief sat at the table with the men from the Dominic drinking the good Scotch

whiskey they had brought. Outside the hut a group of his wives, wearing G-strings and a baby, either fore or aft, did a wild dance. Then they came in, bearing seven goats, and the chief bled the goats into dishes. As the guests left they saw men going through the town smearing blood on gate posts in a reinactment of the Passover.

"You can see," Dr. Blair commented, "why I was not too enthusiastic about the practice of medicine."

Returning, the ship carried troops from the Ashanti War, so that Dr. Blair served as Troop Surgeon, as well as Ship Surgeon in the British Mercantile Service. The innumerable malaria cases aboard, one of them himself, Dr. Blair dosed every morning with hypodermic quinine.

Out of this trip came his first paper, "Malarial and Blackwater Fever." It is interesting to note that Dr. Blair has written at least 22 papers on subjects and in publications not related to plastic surgery. Among these subjects are "Two Practical New Wrinkles in Through and Through Drainage," "A Conservation of the Parietal Motor Nerves in Abdominal Section," "A Suggestion for the Treatment of Air Embolism," "Vein to Vein Transfusion," "An Incubation for Delicate or Premature Infants," and "Surgical Treatment of Pulmonary Tuberculosis."

The paper on malaria was delivered before the Medical Society of the St. Louis City Hospital Alumni and following its publication in the January, 1901, issue of the St. Louis *Courier of Medicine* was later reprinted in pamphlet form. It is notable, not only for its comments on the fevers, but for the fluid interest of its style. "I had not been at sea for six months," it begins, "before my curiosity was permanently piqued by the partly fabled, partly true tales of the wealth, the dismal forests, the great rivers, the savagery, the mahogany, the gold, and the curios of the surf bound, fever stricken west coast of Africa, which has furnished gold, ivory, and slaves to the civilized world from time immemorial."

The later medical pamphlets are not so discoursive, "The Influence of Mechanical Pressure's" two and a half pages being a model of succinctness. But occasionally the style of a person steeped in literary associations is present. In "Nasal Abnormalities, Fancied or Real," which was written with Dr. James Barrett Brown, it is easy to recognize Dr. Blair's style and sense of humor in the opening paragraph. It reads, "When the milkmaid of poetic fancy informed the impertinent observer that her face was her fortune, she unwittingly bespoke one of the fundamental truths of our social contact, a truth that has the greatest emphasis when the face happens to be a misfortune."

Invalided ashore after the African voyage, Dr. Blair's mother and his family called him home. He still had, he insists, no desire to practice medicine but he was 30 and too old to begin something else again. He received an offer to work with Dr. Willard Bartlett and accepted. Dr. Brooks, in that talk referred to earlier, said that he had often heard "Dr. Blair state his everlasting gratitude to Dr. Willard Bartlett for the help he received in emerging from what appears to be a strange training for the attainment of eminence in surgery."

It was shortly after his return that he fell in love with Miss Kathryn Lyman Johnson, daughter of a well known St. Louis doctor. Kathryn, who was then teaching school, was a person of monumental calm, a perfect opposite to the brilliant, versatile, tempestuous Vilray. On their wedding trip she opened her bridal trunk to find a skull that Vilray, lacking other room, had cached there, so that he might continue a study he was making of the jaws. She made up her mind then that, henceforth, nothing would disturb her. Nothing did. At times five children played about her feet, Dr. Blair would pick the middle of the night to brew coffee and talk for hours, guests would come and go, the furniture in the house be arranged and disarranged, but she has remained placid through it all.

In Kathryn's quiet understanding Dr. Blair found his greatest happiness and to her he gave an unending devotion. It was to "my Mrs." or "my Madam," as he called her, that he hastened home. Associates, who traveled with him to medical meetings, or on his numerous trips when he organized the Plastic Surgery Board, say that he always found time to dash to the best store the city afforded to buy a present for "my Mrs." In the many letters which he wrote thanking friends for their congratulations on the occasion of his receiving the honorary degree of Doctor of Science from Washington University for his attainments in science, he never failed to mention his delight in what he called "this unexpected honor" because it had so greatly pleased Kathryn.

When Mrs. Blair suffered a stroke and was partially invalided for the six years preceding her death, Dr. Blair remodeled a two-decker city bus into a home on wheels, so that they might travel together. This unusual conveyance, which he planned and saw executed, accommodated, in addition to the Blairs, two nurses and the chauffeur. It was written up at great detail in the St. Louis papers and in the papers of many of the cities which the "Bus Kathryn" visited.

The responsibilities of a wife and rapidly growing family who "needed more food than I could provide" stopped Dr. Blair's wanderlust. He developed his private practice and taught and counseled in both Washington University's Medical School and School of Dentistry. An incident, which

"A Note on a Surgeon"—sketch of Dr. Blair by Gertrude Hance.

is one of the other family explanations for Dr. Blair's specializing in plastic surgery, occurred at this time. He had an assistant, a pathologist, who had an extremely prognathous jaw. The young man asked Dr. Blair if he would operate on it and Dr. Blair agreed. This, the family say, centered his interest on the mouth and jaw, and he did so much work in the field that as early as 1906 he published three papers and in 1912 the book, "Surgery and Diseases of the Mouth and Jaw."

One of his lifelong friends offered an interesting layman's comment. "He worked with a dentist," the friend said; "he and the dentist figured out what type of face structure goes with different types of teeth so that Dr. Blair, in reconstructing jaws, could start with the teeth. It was a very original thing for him to do."

In the next decade Dr. Blair became Associate both in surgery and clinical surgery at the Washington University School of Medicine. In June, 1917, he took a leave of absence from his various duties to become a Captain in the Medical Corps of the United States Army and was assigned to active duty at Fort Oglethorpe, Georgia. He had only been there a month when the Surgeon General, conferring on the selection of a chief for the Section of Oral and Plastic Surgery, said that "a man from St. Louis had written the best book on the subject," and Captain Blair was promoted to Major Blair, transferred to Washington and made Chief of the Section.

In March, 1918, Dr. Blair became Senior Consultant for maxillo-facial surgery, until December, when he went overseas as Chief of oral and plastic surgery. With him were a group of consultant teams, meant to facilitate the care of face injuries,

one of the most prevalent types of wounds in trench warfare.

The teams were given an opportunity to observe with the French and British, and Dr. Blair says he learned a great deal from the British who had made many advances in plastic work. The friendships he made then he kept for many years.

The teams instituted a plan of early treatment, the great majority of the cases so treated being discharged in France or England. The rate of time between early and late treatment was roughly as months to years.

Dr. Blair took active part in the battles of Chateau-Thierry and the Argonne. He was discharged with the rank of Lieutenant Colonel. After his return home he remained as a Colonel in the Reserve Medical Corps, and served as Attending Surgeon in plastic surgery at the Veterans Hospital at Jefferson Barracks outside St. Louis until 1946. For the following year he was a Consultant at the same hospital, and then he retired.

Dr. Blair's youngest son was born just before he went abroad and he returned to a family of five children. He claims he expected to starve, but his war-time reputation had augmented his civilian one and his practice grew rapidly.

Those were the busy years! The people who worked with him could hardly keep up with him as ideas and plans and suggestions came in a rapid flow. They teased him that he always returned from a period of rest and meditation at the White House, a Catholic Retreat for men, ready to turn the office upside down.

It was at this time that Dr. Blair, almost single-handed, organized the American Board of Plastic Surgery, devoted to raising the standards of practice in plastic surgery and to providing adequate training for qualified young surgeons. Entirely at his own expense he traveled from one end of the country to another, interviewing and interesting many different men, and obtaining recognition for the board.

The posts he held as Associate Surgeon at the three hospitals of the Barnes Group, Barnes, Children's and St. Louis Maternity, had added to them the titles of Honorary Staff Member and Visiting Surgeon at DePaul and St. Luke's, and the St. Louis Mullanphy Hospital. He continued his teaching, being Professor of clinical surgery at the Medical School, and Professor of oral surgery at the Dental School, both of Washington University.

The days were not long enough. There were the articles and books to be written singly and in collaboration, articles that gave the results of months of painstaking work. There was the boy from Seattle born without a nose, without even a nostril opening in the flat plane of his face. That boy has a nose, built up through many operations. He is married and leading a normal life. There was a little girl whose finger had been cut off and who was painfully self-conscious of it. She got a new finger, made from her toe. There were the babies with harelips, the faces that had been destroyed by cancer, the hands with no fingers, the eyes with no lids, the bodies with whole areas of surface destroyed by burns.

There was little in the long list of human disfiguration that did not come into the office, come from St. Louis, from all over the country, from much of the world. For, of all Dr. Blair's patients in the best beds and in the wards of Barnes, only seven per cent came from St. Louis. The rest came from everywhere.

It was at this time that Dr. Blair developed his skin grafting knife and vacuum retractor, the uses of which are described in his paper on the "Use and Uses of Large Split Skin Grafts of Intermediate Thickness." This paper did a great deal to awaken the profession to the possibilities of the rapid and satisfactory closure of large open wounds.

During all the years of his practicing he was influencing and training younger men, giving them generous cooperation as well as instruction. In Dr. Sumner L. Koch's recent article in "Plastic and Reconstructive Surgery," he says of Dr. Blair: "If the measure of a man's success from a surgical and scientific viewpoint is determined by the men he has influenced and trained we have only to look about us to realize how profound an influence Dr. Blair has exerted upon the practice of plastic surgery. The late Earl Padgett, Brown, Webster, Hamn, Byars, Cannon, MacDowell . . . to mention only those on the roll of our association . . . are 'passing on the torch' and bringing increasing credit to their preceptor."

A person in a related field who feels she owes much of her development to Dr. Blair is Miss Gertrude Hance. As a young artist in the field of medical illustration, she was called in by Dr. Blair. With his advice she took further courses in anatomy and sculpturing, so that she could do his medical illustrating, and make models of the faces he was to reconstruct. She also made plastic noses and ears for patients to wear while their own were being rebuilt. At Dr. Blair's suggestion, Miss Hance developed a new method, based upon tattooing, for the permanent injection of color into flaps and grafts of skin used to repair the face and lacking the face's ruddy color. She has since trained an army artist to do the same work in army hospitals.

Still working with Dr. Blair's office, Miss Hance remembers with fond amusement the days when she started with him. "He went so fast," she says, "that I could hardly follow. I would trot to keep up with his long strides and I would listen frantically trying to keep up with his ideas.

"I was very young and afraid to answer back

when we disagreed. It took me a long while to learn that Dr. Blair likes to be talked back to. It is amazing when you think how modest he is about his medical accomplishments, how imperious he is about his ability to run your life. I have never heard him say any work he did was good, for he had already thought of a way he could have done it better, but he certainly thought he knew what was best for me, for his children, and for all the people who worked with him.

"He is a very devout Catholic. It used to worry him that I wasn't a devout Methodist and that I didn't go to church every Sunday. I did almost everything he told me but he never made a real church-goer out of me."

OTHERS who worked with him delight in talking of Dr. Blair. He is famous for his humor. He would dictate to his secretary while looking out of the window at the people walking on Grand and Olive, a busy thoroughfare, below his office in the Metropolitan Building. One day a woman came by wearing a skirt with three tiers. Dr. Blair, hardly stopping, said wistfully, "I wish she'd drop a tier."

He has the quick temper that so often marks the surgical virtuoso. He never battered down an elevator door, as did one of his Barnes contemporaries, furious at being kept waiting, but he has been known to kick over a tray of instruments. He sent the operating room nurse flowers the next day, as quick to remorse as he is to rage. He must have kicked sideways, because he operated sitting down, so that the patient's head often "looked as if it were in his lap."

His patients adore him. But though they had the deepest consideration from him he never remembers their names. "Who was that?" he will ask when someone brings him a message from, or tells him news of a former patient. The operation he remembers but the personality he forgets. Yet he early recognized the value of psychiatry in surgery. In an unwritten talk, given before the Southern Neuropsychiatric Society on "Observations of Psychic Manifestations in Surgical Cases," he said, "From observation and experience and not from special study, I have come to believe there is no part of the body in which an aberration may not be the primary cause of a neurosis." In his own special field the cure of a neurosis caused by a repugnant deformity was often as much a part of his work as the operation which remedied the abnormality.

His accomplishments added a great deal to the growth of the reputation of Barnes and of Washington University Medical School. He has retired from them now, and from his office, but in many ways he is still very much present in all of them. For his surgical brilliance and courage, for his humor, for his modesty, for his ability to teach, and his willingness to befriend young men, for his sheer physical presence, Dr. Blair has become that rare thing, a legend in his own time.

MIRIAM TUCKER

SISTERS OF DARKNESS VERSUS MODERN MEDICAL SCIENCE

THE BELIEF of antiquity that man's fate lay in the hands of the gods is symbolized in this month's cover painting by Edmund Kopietz. To the trio of mythologic fates, however, has been added a more modern triumvirate whose pioneer work in making childbearing safer has served to lengthen the thread for countless mothers and infants.

In Greek and Roman mythology the fates—Klotho, Lachesis and Atropos—were characterized as three sisters, daughters of Night, to whom Jupiter allotted the function of determining the lot and length of mortal life. The fates were usually shown as three women, wearing woolen chaplets interwoven with flowers of the narcissus and occupied with their tasks: Klotho, the spinner, Lachesis, measuring the span and Atropos, ready with the scissors to mark the final cutting.

Reprints of the cover, suitable for framing, may be obtained from *Postgraduate Medicine*, 516 Essex Building, Minneapolis, Minnesota. Price: $1.00.

IPMA PRESIDENTIAL ADDRESS

I Wish I Knew—or an Analysis of Hobbies

(SCIENTIFIC AND OTHERWISE) — OR THE ADVANTAGE OF MULTIPLE HOBBIES OR ISN'T WORK EASIER?

WALTMAN WALTERS*

MAYO CLINIC, ROCHESTER

When I was 11 years of age I began playing golf with a driver, brassie, midiron, lofter, a brass putter and three Spaulding red dot golf balls. Each club cost $1.50. I bought a new midiron two years later with the profits I made from taking and selling pictures of the eighth grade at Bancroft Grade School (Omaha). I took these pictures with a Brownie No. 2 box camera which cost $2. I developed film and printed the pictures which I sold for 10 cents each. After I had sold 15, I had enough money to buy the A. H. Wright midiron which I used until 10 years ago. Thus developed two hobbies which I have continued with great pleasure, enjoyment and profit.

As time passed, the expensive, and I sometimes think the promotionary, acquisition of nine so-called matched golf irons of similar weight and appearance but with a different angle became almost a necessity. With a golf stroke of similar force the angle that the face of the iron makes with the ground determines the loft of the ball and hence the distance the ball will go if the stroke is accurate and the ball is cleanly hit and goes in a straight trajectory. The number of matched wooden-headed clubs of different weights and sizes and lofting angle of their faces which I acquired increased from two to three and then to four and now some players, including me, have obtained a number five wood. The cost of each matched iron now varies from $6 to $10 and each wood in the better matched wood sets retails for $10 to $20—making an investment in golf clubs of about $140.

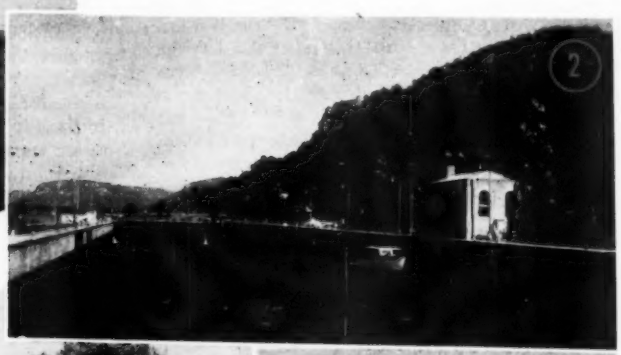
Now all average golfers know that seldom does one play well during any one round with both woods and irons and practically never with woods, irons and a putter. Thus with a set of four or five wooden clubs and a set of nine iron clubs (both matched) in the golf bag if one is not playing well with the irons, one can play the woods and vice versa. Whereas, there used to be but one conventional type of putter, there are now many, iron, wood, aluminum, brass—straight putters, mallet putters, even a putter with a looking glass on it; so every golfer must have at least two. When all of these clubs are put in a bag it is necessary to have a caddie or a go-cart to carry the bag and clubs. These carts are now available for rent on all good courses.

The interesting feature about this is that my score was as good when I used a set of five or six clubs which I carried in a light canvas bag, costing $3, as it is now when I use 14 clubs carried in a heavy leather bag, costing $40, equipped with pockets large enough to accommodate shoes, underwear, an umbrella and even a suit of clothes. When caddies and golf carts are not available, the light canvas bag with five or six clubs is substituted and the golf score is about the same as when I use the complete set carried in a heavier bag pulled or sometimes pushed in a go-cart. Now the question is: Do these expensive developments improve the enjoyment of the player in the game? Does the golfer play a better game? Does his decision (of course, after consultation with his caddie) to use a five iron instead of a four or six, mean that he is playing a more scientific game? This seems to me to be an important problem to speculate on during one's leisure.

Forty-three years ago, the golf stroke then in vogue demanded that the player wrap his club and his arms around his neck in the golf wind-up. Only former baseball players who had taken up golf in their middle age kept a reasonably straight arm and forearm during the backswing, and all the young onlookers would comment that he would never be a golfer because "he swings as if he were swinging at a baseball." However, he would usually hit the golf ball hard and long. Now, all golfers know the value of the straight left arm and forearm with the stiff elbow and the cocking of the wrists. Uncocking the wrists gives force to the stroke and increases the pressure of impact of the head on the ball. Moreover, pictures of the leading home-run ball players show an almost exactly similar straight left arm and cocking of the wrist in their backswing.

This leads to the other interest I referred to,

*Presidential Address read at the 35th Annual Assembly of the Interstate Postgraduate Medical Association, Chicago, and Mayo Foundation Chapter of Sigma Xi, Rochester, Minnesota, June 1, 1950.



1. Golfing companions, Tucson Country Club. Catalina Mountains in the distance. 2. One of the series of 27 locks between Minneapolis and New Orleans with small cruiser in the lock. 3. Trees and foliage with channel marker on the Wisconsin side of river below Wabasha. 4. Twin-screw diesel-driven Mississippi river towboat in the distance pushing loaded oil barges up the Mississippi. 5. Widening of the Mississippi as the result of the dams maintaining the 9-foot channel. Notice channel marker with number of miles above St. Louis. 6. Old time stern wheel Mississippi river towboat.

namely, photography. Having taken good pictures easily and cheaply with a Brownie No. 2, I graduated to a folding bellows type of camera which cost 10 times as much and with which it was 10 times harder to get good pictures because my guesses of the distance from lens to object were just far enough off to blur the picture. But after a while by pacing off the distance this error was usually avoided. This type of camera was too large and heavy and the miniature camera became the rage. With this camera the need of accurate focusing became more apparent. A miniature picture slightly out of focus became exaggerated when the small films were enlarged or blown up—this led to the development of the range finder. With accuracy of focus obtained, one was confronted with the great variability of contrast in prints—they were either too light or too dark and then the light meter was developed. With an expensive miniature camera which took pictures on a film so small that enlargements always had to be made, with an attached range finder and a $25 light meter I was able to get about as good a picture as I used to get and still do with a box camera if there is enough light to take an instantaneous exposure of not over one-twenty-fifth second.

Now what I wish to know is: Whether the amateur photographer who has accumulated all the elaborate paraphernalia and intricate scientific instruments to take clear pictures is happier than the man who gets equally good pictures under reasonably similar light conditions with a cheap fixed-focus box camera? Or is he happier because when he gets as good a picture with an expensive miniature camera he considers it as an accomplishment since he has so many odds against him?

Looking at golf and amateur photography as I do, I am sure you wonder why I like golf and photography. The answer is that golf is a game which takes patience to learn, it is played over beautiful country with congenial companions and usually it can be played all of a person's life. Photographs also can be taken indefinitely. Golf requires physical exercise and skill. Photography can be done if physical exercise is forbidden; moreover the pictures are a splendid record of good times which can be shared with friends (Figure 1).

When I was young and had six golf clubs, I occasionally shot less than 80 (for those of you who are not golfers that is the crowning achievement of the occasional golfer), but in these later years I have broken 80 only four times, twice, however, at the Rochester Country Club. The first time that I did this (about 10 years ago), I had more men slap me on the back and congratulate me than had done so over a 20-year period on my total surgical contributions, if any, to that date. One wonders if we are taking our golf seriously enough? The size of this platform doesn't permit a demonstration of my golf stroke, but I do have an exhibit of some of my earlier clubs and a set of matched irons which I bought last week, just 43 years after starting my golf.

As an example of my 43 years of—and still superficial—knowledge of photography I thought you might be interested in seeing a few photographs which have pleased me: (1) a rainbow after a spring storm in the Catalina Mountains at Tucson, Arizona; (2) five minutes later.

You are probably wondering when I am going to launch a detailed scientific discussion of my hobbies. When I was a medical student we were told by mouth and by writ that it would pay all of us to develop a hobby and really work hard at it. But isn't it better to have several? If you tire of one or are unable to pursue it because of change of mind, conditions of health or availability of time, accessibility of place or of materials you can have fun with another. Having always been interested in rivers, lakes, oceans and even swimming pools, it has been my delightful experience to be a Minnesota week-end (lest you misunderstand, mid-Saturday afternoon to Sunday evening) "Mississippi River Rat." This is an affectionate term given to men who love the river or live on it in a boat or on its shores in anything from a shack to a cottage, but usually a shack.

Rochester is just 36 miles from the longest and probably in its upper third, the most beautiful navigable river in the world, the Mississippi. "Missi" is Chippewa Indian for "great," and "sippi" is "river." This great river is 2,550 miles from its source in Lake Itasca (Latin for true head) to its mouth in the Gulf of Mexico. It is navigable with a nine foot channel from Minneapolis to the gulf, a distance of 2,037 miles. From Red Wing to LaCrosse, probably the most scenic portion of the river, with its beautiful wooded banks rising to plateaus it takes a circuitous course so that during that entire distance it is only about 50 miles from Rochester. The river drains a third of the United States, an area of 1,243,000 square miles. It and its forty-five navigable tributaries are open to commercial navigation for 15,000 miles. The river and one of its lakes, Lake Pepin, is right at my doorstep. Its beauties can be enjoyed by row boat, canoe, sail, or motor boat or raft. Because of its current or long distance between towns its waters are clean, it has many edible types of fish waiting to be caught, it is pure enough to swim in with safety, yet how few people know of its charm or enjoy its wonders.

When I consulted one of my friends concerning a topic for the Presidential Address for the Mayo Foundation Chapter of Sigma Xi he said why don't you talk to them about the Mississippi River and show them some pictures of it and its banks

and its boats. So we will start out from Rochester along route 63 and see some pleasant rural scenes such as these of the wheat fields, and soon we come to Lake Pepin at Lake City. From there we travel down the lake into the river at Reads Landing, and then on past Wabasha to the Alma (Wisconsin) dam and locks. There are 27 dams with locks between Minneapolis and the Gulf of Mexico which give the wide river and the nine foot channel. The building of these dams and locks began in 1930 and is now complete. There are 12 locks above Minneapolis (Figure 2).

The Chippewa River arising in Wisconsin joins the Mississippi just above Reads Landing forming a delta which is the cause of Lake Pepin, 21 miles long and three miles wide. In many places especially above Minneiska (15 miles below Wabasha) damming of the river has made an artificial lake. The channel is well marked. Red and white buoys with pointed tops mark the east side and black and white ones with truncated tops the west side (Figures 3 and 5). There are the shore markers of crossed white boards or white concrete six-sided markers in the river, with automatic lights flashing twice on the east and once on the west, with numbers on them indicating the number of miles north of the entrance of the Ohio into the Mississippi. In the early days coal burning steam propelled stern wheelers pushed barges containing coal, gasoline and farm machinery up the river (Figure 6). These have given way to oil burning diesel engine barges with twin-screwed propellers; these powerful ships push six to eight barges in tandem (Figure 4).

It might be well to speak of a fine river, the St. Croix, which arises in Wisconsin, becomes a lake at Stillwater and empties into the Mississippi at Prescott, Wisconsin, a few miles below Hastings. The lake is 23 miles long, is from 30 to 100 feet deep and its water is clean, blue and deep. North of Stillwater on the St. Croix River is Taylor's Falls and the St. Croix Dells. It is 52 miles between these cities and the river scenery is very beautiful. Near Taylor's Falls the St. Croix River is surrounded by sheer cliffs. Between these cities the river is navigable but the channel is not marked. For small boats it is best to make the trip downstream in the spring when the river is swollen with the spring floods. Another tributary of the Mississippi, the Zumbro, Indian meaning coiled snake, which rises in southern Minnesota, empties into the river two miles below Wabasha.

The high banks of the Mississippi are covered with trees. In the fall the foliage along the river changes. The leaves begin to turn yellow, then red.

When one is on or near water one must have something to do such as boating, fishing, or swimming. For example if you have a small boat on which you can sleep overnight, keeping it in good condition will keep you in condition. It is like horseback riding, "The outsides of a horse are good for the insides of a man."

If one fishes, the purchase, assembly of one's equipment, the throw of the artificial bait into the water as one sits at anchor or slips slowly down the river keeps one interested even though one doesn't catch a fish. I was once characterized by my wife as a fisherman but not a catcherman after fishing the Mississippi River for one entire summer without catching a fish. I used, of course, a fly pole, waxed line, automatic reel and artificial yellow coachman fly. Curiously enough everyone I passed fishing with a bamboo pole with fixed line and using angleworms as bait on a plain hook, seemed to be catching fish.

One time one of my colleagues was with me who had never fished with a fly rod line and artificial fly. He suggested that he might like to try casting it out and did so after some discouraging remarks on my part. He made an awkward cast and the bait and hook landed only a few feet from the boat. His cast didn't compare with my perfectly placed 25 or 40 foot casts but he caught a three-pound small mouth bass.

The implication is obvious, I believe; why do we make things hard for ourselves when we try to enjoy ourselves—especially when simple, easily obtained equipment seems to do just as well.

After a hard day of golf, when the course seems more difficult than usual, or a hard weekend on the river when I return without fish and with skin-barked hands, a sore back and sunburned face, as I leave the river or golf course with the shadows lengthening and the sun sinking and the colors of the sunset spectrum fading from the skies, I long for the hustle and bustle of the consulting room corridors of the clinic and for the quiet of the operating rooms of our hospitals.

There is a framed motto hanging on the wall in the corridor leading to the Board of Governors Room put there by Dr. W. J. Mayo: "There's no fun like work." I used to wonder about that motto 30 years ago; now I believe it sincerely, but I think one could improve it by adding the word "happy" work. "There is no fun like happy work" is from the *Map of Life,* written by Lecky in 1899. I would like to quote a few short passages from it. "One of the great differences between childhood and manhood is that we come to like our work more than our play" and "one of the first conditions of a happy life is that it should be a full and busy one. . . . Pleasure is a jewel which will only retain its lustre when it is in a setting of work. . . . A vacant life is one of the worst of pains though the islands of leisure that stud a crowded, well-occupied life may be among the things to which we look back with the greatest delight."

Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Subscribers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board and our Editorial Consultants best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 516 Essex Building, Minneapolis 3, Minnesota.

EFFECT OF CONTINUED ESTROGEN ADMINISTRATION

QUESTION: Please advise as to the effects of estrogen administration, by injection, averaging approximately 1 mg. per week for eight years, in a patient who has menstruated fairly regularly during all these years. I am particularly interested in whether tachycardia and a chronic P.M. low grade fever can occur.

These objective findings have been corroborated by several recognized clinicians with no diagnosis having been made.

M.D.—Tennessee

ANSWER: The chronic administration of estrogen in the dosage level mentioned does not as a rule disturb cyclic menstruation nor is it sufficient to markedly alter pituitary activity. In the opinion of this consultant, the tachycardia and the low grade fever are not related to the administered medication.

ROBERT B. GREENBLATT

GLUTAMIC ACID IN TREATMENT OF CEREBRAL PALSY

QUESTION: I have a patient 14 years old who has cerebral palsy with moderately severe involvement of the extremities but very little involvement of speech. He does poorly in school, and his parents want to know whether glutamic acid will help him.

Has glutamic acid been tried in these cases with any success? I would also like to know what facilities there are in this area for (1) mental and psychologic testing of these cases; (2) muscle education, speech training and other rehabilitation of these patients.

M.D.—Minnesota

ANSWER: Improvement in intelligence has been reported by some workers following administration of glutamic acid to children with mental retardation. No direct effect upon the motor impairment has been claimed. Psychometric examinations are made by psychologists working in this field. Such persons are known to most psychiatrists. Examination can also be arranged at the University of Minnesota in the Department of Child Study.

Regular programs of psychical training for the cerebral palsied are carried out in special schools in the larger cities of Minnesota. Instruction in training also can be secured by consultation with private therapists through doctors working with cerebral palsy. The State Bureau for Crippled Children also maintains a service, largely for instruction of parents in physical and speech training, which is available to smaller cities and rural areas.

JOHN F. POHL

INDICATIONS FOR CHOLECYSTECTOMY

QUESTION: Please advise me as to the proper handling of the following case, and if cholecystectomy is indicated.

A female patient, about 40 years of age, rather obese. Symptoms are upper abdominal pain, lasting two weeks or more on two occasions two years apart and associated with some emotional strain. She was relieved on the first occasion by the restriction of fats in her diet and a general reducing diet. Later she failed to respond to this procedure, but the pain gradually subsided. However, at no time did the pains amount to a definite gallbladder colic. They were rather constant, with some exacerbation at night.

The gallbladder fails to visualize after priodax. The same procedure was performed during the first attack and repeated after symptoms of the second attack two years later had subsided. Gastrointestinal series is negative.

M.D.—Virginia

ANSWER: Chronic cholecystitis with associated cholelithiasis may not lead to the typical colic-like pain frequently associated with gallstones. In the absence of signs of pathology demonstrable in the gastrointestinal and genitourinary tracts, the symptoms outlined indicate pathology in the gallbladder.

One should not advise a cholecystectomy in the absence of stones, but with these findings they will usually be present. Intermittent cystic duct obstructions have caused the two attacks of upper abdominal pain. In the absence of other causes for symptoms and with nonvisualization of the gallbladder on two occasions, a cholecystectomy should be advised and should result in complete relief of symptoms.

RICHARD B. CATTELL

ALLERGY TO STREPTOCOCCUS ORGANISMS

QUESTION: Please discuss allergy to streptococcus organisms as to diagnosis and treatment.

M.D.—California

ANSWER: Diagnosis is based on a careful history, physical examination and the recovery of a virulent strain of streptococci from the nose, throat, sinuses, bronchial tubes or infected teeth.

Treatment should consist of the surgical elimination of all foci of infection plus hyposensitization with stock or autogenous vaccine, starting with a very small dose (1/20 cc.) and gradually increasing the dose until 1 cc. is given. This top dose should be continued at intervals of two weeks until all of the symptoms have been controlled for at least a year.

HARRY L. ROGERS

"MACERATED FETUS"—DEFINITION

QUESTION: In discussing a paper about "Prolonged pregnancies and macerated fetuses," there has been a doubt by some just what is the accepted definition of "maceration." The standard medical dictionaries define maceration "softening by the action of a liquid," and macerate "to soften by soaking."

In my paper I stated I had delivered many macerated fetuses dead and lately I had delivered three live babies with maceration, who are now living. The hands, feet and parts of the body had some desquamation, especially the hands and feet, which were like a washerwoman's hands, that had been soaked for some time. There was no vernix caseosa, amniotic fluid, and only a small amount of a brownish green substance and meconium. Two of these cases showed positive signs of prolonged pregnancies, the other a toxemia with ample fluid.

My contention is that the peeling of the skin was desquamation, caused by maceration. I believe the skin had to soften before desquamation.

Several pediatricians tell me they associate maceration with necrosis and death and there is no such thing as a live macerated baby. Still others tell me to clarify my terminology with definitions, and this would eliminate the haphazard reader who is usually not a student.

I find very little about maceration in the textbooks and literature. Runge, of the Frauen-Klinick, Heidelberg, states in his paper, "Protracted Pregnancies," that these babies have a high mortality rate, if they survive that long. His illustrations show live babies with maceration.

I would appreciate your help by telling me what you consider is maceration and if in your experience you have seen any babies with maceration living.

M.D.—New Mexico

ANSWER: One becomes entangled in the various interpretations of a definition quite often. The term "macerated fetus" has come to denote a stillborn infant, dead in utero for a time sufficient to allow postmortem changes leading to exfoliation of the skin. Minor degrees of "softening by the action of liquid" of the skin of the palms of the hands and soles of the feet are commonly observed in healthy live-born children.

INTRAVENOUS USE OF MERCURIAL DIURETICS

QUESTION: Information is requested regarding the intravenous use of mercurial diuretics. Neptal was used in a man who was in moderately advanced congestive heart failure; death ensued about one minute after intravenous injection. This man had myasthenia gravis and myocardial infarction three months ago. Safety factors—dilution, intramuscular route, slowness of injection—are used. Using the intravenous route, what other safety factors could be used along with the Neptal? Atropine? Quinidine? Benadryl? Ascorbic acid? One per cent procaine?

M.D.—Ontario

ANSWER: It is my belief that rarely is it necessary to use mercurial diuretics intravenously. They should never be used unless a small dose is given subcutaneously to test the patient for sensitivity for whichever of the drugs is used. The preparation about which the inquiry is made, Neptal, I know nothing of. Sudden deaths are reported from the intravenous use of other mercurial diuretics in advanced congestive heart failure. This does occur even when patients are previously tested to see if they are sensitive to such a drug.

It is my belief that intravenous medication of any kind should not be employed when it is possible to give a remedy intramuscularly or subcutaneously. When the intravenous method is chosen, the agent or drug which is used should be well diluted from 20 to 50 times. It should be injected very slowly—at the rate of 20 to 30 drops a minute. Insofar as I know, other drugs which are useful in overcoming the bad effects of intravenous mercurial diuretics are of little value because the patient dies before they can be given. While there isn't any direct evidence that such a thing can be proved, yet it is possible that this type of medication may provoke a ventricular tachycardia which causes sudden death.

JAMES E. PAULLIN

TOXICITY OF CALCIUM BROMIDE

QUESTION: Older medical handbooks recommend calcium bromide as being a sedative to nerve centers, but less depressing to the heart than other bromides. However, it seems that calcium bromide is now rated as being toxic and unsafe according to some views. I wonder why. Kindly give me the correct information on this question.

M.D.—Tennessee

ANSWER: Calcium bromide has no particular advantages or disadvantages over other bromides. As it is very hydroscopic, the solid form is unstable. The amount of calcium in the usual dose is small and exerts little effect upon the human body. The references to the toxicity of calcium bromide may be on the theoretical ground that calcium enhances the action of digitalis upon the myocardium. Thus, in a fully "digitalized" patient, poisoning might occur. This seems very unlikely.

It would seem reasonable to give the more stable bromides as sedatives. If calcium is needed, it can be given in more conventional forms such as calcium lactate or calcium gluconate.

MORRIS W. STROUD, III

ISOTONIC DOUCHE

QUESTION: What isotonic douche (constituents) would be helpful prior to intercourse to overcome a vaginal *pH* which might be preventing conception?

M.D.—Ontario

ANSWER: Variation of the *p*H of vaginal secretion as a cause of infertility is debatable. Inasmuch as this secretion is normally on the acid side, it is common practice to prescribe a 1 per cent solution of lactic acid or vinegar as a precoital douche.

(Continued from page 10)

years, who had acute palindromic arthritis of the right hand. The intravenous administration of histamine according to the same method employed in the case of acute gout (case 5) relieved the pain within 12 minutes.

Although the subcutaneous administration of 0.3 mg. of histamine base as a provocative test in an attempt to reproduce the pain in the left side of the head in case 5 produced substernal distress, the intravenous administration of histamine diphosphate did not cause any discomfort whatsoever.

Although the patient received 35 additional injections of histamine in an attempt to eradicate the headache, he could still precipitate pain in the head by sneezing or coughing. However, he noted that he could walk a distance of 2 or 3 blocks without the development of substernal distress whereas, when he first came to the clinic, he could walk only a block before the pain developed.

I had previously had occasion to treat a man, aged 55 years, with acute gout, in this same manner on May 24, 1943. The patient was brought to my laboratory in a wheel chair at 10:30 A.M. because of acute gout involving the metatarsophalangeal joint of the left foot. The attack had begun at 9:30 P.M. the previous night. There was redness and edema of the involved joint. Histamine was administered intravenously according to my standard method at rates ranging from 30 to 60 drops per minute. Treatment was carried out for approximately an hour and a half. The redness and edema of the joint largely disappeared and the patient could walk at the end of his treatment, and he had only a slight limp. On the following day, the left foot was normal. This patient had had previous attacks of gout, and the average attack had confined him to bed for about seven days.

WHAT is the mechanism for the relief of pain in acute gout? It is most probably due to the action of histamine on the suprarenal cortex, causing the release of cortisone. This seems probable since the relief of pain occurs promptly and corresponds with the drop in the eosinophil count of the peripheral blood within 20 to 40 minutes after starting the intravenous administration of histamine.

Case 6. Penicillin reaction—A boy, aged 14 years, underwent an operation for chronic osteomyelitis of the left femur at St. Marys Hospital on June 11, 1945. To combat infection, penicillin was given in rather large doses for six days prior to, and for four days after, the operation. A penicillin reaction developed on the fourth postoperative day, and the administration of the drug was discontinued.

When I saw the patient at 3 P.M. on June 18, 1945, his face was greatly swollen and the itching was severe. Generalized swelling also involved the 4 extremities. His hands were stiff, and he had difficulty in making a fist. He had some difficulty in swallowing, and his vision was somewhat impaired. On the right leg, the urticaria had a serpentine appearance. The left leg was completely enclosed in a cast. Frequent injections of epinephrine and the intravenous administration of calcium gluconate had not relieved the symptoms. He had had a similar penicillin reaction the previous year when he was under observation at the clinic.

Intravenous administration of histamine diphosphate at the rate of 48 drops per minute was started approximately 78 hours after the onset of the penicillin reaction. Symptomatic improvement occurred promptly, and, after the injection had been continued for an hour and a half, he remarked, "I can see much better." The swelling of the face had definitely decreased, and by 10 A.M. the following morning (less than 24 hours after the first injection of histamine), the urticaria had largely disappeared and the serpentine areas on the right leg were completely gone. The itching had ceased, and he was able to swallow without difficulty.

Comment on Case 6—This is the third case of penicillin reaction in which I have obtained satisfactory results by the intravenous administration of histamine prior to June, 1945. This is still the simplest and most efficient type of therapy for a penicillin reaction. It is preferable to the administration of antihistaminic drugs since it does not produce side reactions so frequently and it produces relief more promptly.

Case 7. Headache of indeterminate type—A woman, aged 44 years, came to the clinic on February 16, 1942. She had been entirely well until December 27, 1941, when she awakened with a severe headache, which had been pulsating in nature, had originated in the posterior part of the neck and occipital region on the left side, and had extended over the back of the head to the vertex. It had been continuous day and night since its onset, and acute exacerbations had occurred at approximately weekly intervals. Large amounts of morphine had not relieved the pain. She had not noted any personality changes herself, although her friends had noted increased irritability and tenseness. Her head had felt heavy and had seemed twice its normal size. Swelling about the left eye and enlargement of the cervical lymph nodes on the left side had been observed at the onset of the headache. Some black and blue spots had been present on the body and especially on the left hand. The hand had been swollen, black and blue, and the pain in it had persisted for several weeks. The other spots on the body had caused her little or no discomfort. Her family physician had thought she had a ruptured blood vessel behind the left eye.

When she was examined at the clinic, she had a masklike facial expression, staring eyes, and sat rigidly on a chair. She was 61½ inches (156.2 cm.) tall and weighed 141 pounds (64 kg.). The results of neurologic examination were essentially negative except for the presence of a positive Babinski reflex and ankle clonus, grade 1 to 2, on the right side. The reflexes were hyper-reactive on both sides. The blood pressure was 136 mm. systolic and 78 mm. diastolic. Routine laboratory tests, examination of the cerebrospinal fluid,

electroencephalography, and roentgenographic examination of the head, accessory nasal sinuses, thorax and stomach did not disclose any significant abnormality.

Cauterization of the left sphenopalatine ganglion did not relieve the pain, and the intravenous administration of 5 cc. of Kendall's whole cortical extract definitely aggravated it. On the following day, an 0.0011 per cent solution of histamine diphosphate was administered intravenously at the rate of 36 drops per minute. This produced a dramatic change in the clinical picture. Before the first injection had been completed, the patient changed very promptly from a somber, depressed woman to a cheerful, friendly one. She volunteered the statement, "I feel like laughing and giggling; it seems like heaven." She said that she felt as if she had taken "laughing gas." Her headache was entirely relieved for the first time since its onset, and she had the first full night's rest since she had become ill.

She returned to the clinic four months after her dismissal, as she had been requested to do. About two weeks after she was dismissed for the first time, the pain in the left side of the head recurred in its full intensity. It was associated with diplopia and vomiting but not with nausea. Hypodermic injections invariably had made her drowsy but had not relieved the pain. She had undergone a psychiatric examination in the meantime, and the psychiatrist had suspected the presence of an expanding intracranial lesion. The results of complete neurologic examination at the clinic were identical with those obtained at the time of her previous visit. The cause of the syndrome was still obscure.

Comment on Case 7—The marked improvement which occurred during the first intravenous injection of histamine leaves no doubt as to the relationship between treatment and symptomatic improvement. It could hardly have been more dramatic. Perhaps this case illustrates, as much as any other, the wide range of histamine therapy.

Case 8. Diffuse arterial disease, angina pectoris, and occlusive arterial disease of the left lower extremity—A man, aged 43 years, came to the clinic on February 23, 1948, primarily because of angina pectoris of one year's duration and intermittent claudication of the left lower extremity of seven years' duration. Both types of pain were exercise phenomena and were relieved by rest. Since substernal distress invariably had occurred if he walked fast, he purposely refrained from doing so. He had smoked 30 to 40 cigarettes daily since the age of 16 years. There was no history of superficial thrombophlebitis. The arterial pulsations in the upper extremities were within normal range, but the pulsation of the left ulnar artery was difficult to palpate. The pulsations of the right lower extremity were within normal range, but no pulsations were present in the left popliteal space and only faint pulsations could be detected in the left dorsalis pedis and posterior tibial arteries. Definite blanching of the distal half of the left foot was noted when the feet were elevated and exercised, but there was no pain in the left foot. When the feet were in a dependent position, slight rubor, grade 2, of the left toes developed.

His blood pressure ranged from 130 to 162 mm. systolic and 85 to 98 mm. diastolic. Urinalysis did not disclose any abnormality. The concentration of hemoglobin was 13.7 gm. per 100 cc. of blood. The erythrocyte count was 4,340,000 per cubic millimeter of blood, and the leukocyte count varied from 10,200 to 8,800. The differential leukocyte count was normal. A routine serologic test did not disclose any evidence of syphilis. The sedimentation rate of the erythrocytes was 27 mm. in one hour. Roentgenograms of the thorax and left leg were normal. Roentgenographic examination of the spinal column disclosed slight hypertrophic changes in the lower part of the thoracic segment, and slight calcification of the abdominal aorta and pelvic vessels. Examination of a 24-hour specimen of urine did not disclose the presence of lead. On February 24, 1948, an electrocardiogram revealed a rate of 73 with sinus arrhythmia and ventricular and auricular premature contractions. The amplitude of the QRS complexes was diminished in the standard leads, and the T wave in lead I was inverted. In precordial leads V-1 and V-3, the ventricular complex was essentially a QS deflection and in V-5 A-W type complex associated with inverted T wave. This electrocardiogram could be interpreted as showing evidence of previous anterior myocardial infarction.

When the patient was examined at the clinic, intermittent claudication developed in the left lower extremity after he had walked 210 steps at a rate of 120 steps per minute. Pain of an anginal character also developed in the left arm and thorax at about the same time. Rest relieved these symptoms. This observation was made with the patient exercising under controlled environmental conditions and with the temperature at approximately 70° F.

The patient remained under my observation as an outpatient for about two and a half months, during which time he received daily intravenous injections of histamine diphosphate. This drug was administered in the hope that it might improve the circulation of the left lower extremity. Plethysmographic studies were carried out by Dr. Wakim of the Section on Physiology at the time treatment was first started and again at the time of the patient's dismissal. The rate of administration of the drug was 80 drops per minute for the first 30 injections but it was increased to 100 drops per minute during the last 21 injections. When the rate of administration was increased, 100 per cent oxygen was administered by mask during the injection.

Claudication tests were carried out at the same time of each day in the corridors at St. Marys Hospital, where the environmental temperature remained more or less constant. The speed of walking was the same each day, and a physician walked with the patient, keeping a constant check on him. The claudication test did not disclose any evidence of improvement in the patient's ability to walk until after the twenty-third injection of histamine was given. From that time on, there was steady improvement, and when the patient was dismissed he was able to walk a distance of 1,600 steps at the same rate and under the same environmental conditions without the development of intermittent claudication or thoracic pain. He remarked that "at night the left leg and ankle no longer freeze as they formerly did." At the time of his dismissal, sweating of his feet was noted, whereas, prior to treat-

TABLE 1

CONCENTRATION OF PLASMA LIPIDS AT TIME OF FIFTY-FIRST INJECTION OF HISTAMINE IN CASE OF DIFFUSE ARTERIAL DISEASE, ANGINA PECTORIS AND OCCLUSIVE ARTERIAL DISEASE OF THE LEFT LOWER EXTREMITY (CASE 8)

LIPIDS	CONCENTRATION, MG. PER 100 CC. OF PLASMA		
	Immediately before administration of histamine	*During administration of histamine*	*Immediately after administration of histamine*
Cholesterol	217	203	232
Cholesterol esters	136	120	141
Phospholipids	232	195	223
Fatty acids	366	404	365
Total lipids	583	607	597

ment, he had never had any sweating. The results of the plethysmographic studies indicated a definite increase in blood flow to the lower extremities during the time the histamine was being administered.

Another electrocardiogram made at the time of the patient's dismissal, revealed essentially the same findings as recorded on admission, except that the T wave in lead I was isoelectric, as it was in V-5. The absence of the R wave in V-3 continued as the evidence of anterior myocardial infarction.

Table 1 shows the concentration of plasma lipids immediately before, during, and immediately after the fifty-first injection of histamine. The patient was in a basal state while the blood was being withdrawn for the determination of the concentration of plasma lipids. In the light of my present knowledge, I cannot completely interpret the significance of the changes in the concentration of the plasma lipids.

Seven months later, the patient returned to the clinic for additional observation. He said that he had been in excellent health, and that on some days he could walk as much as 10 miles without the development of any symptoms whereas on other days he might have to stop because of heaviness in the thorax or stiffness in the legs after he had walked only 1 block. There was little or no change in the clinical picture. His blood pressure ranged from 140 to 170 mm. systolic and from 86 to 90 mm. diastolic. The electrocardiogram showed sinus rhythm with standard leads showing essentially normal findings. The precordial leads showed an abnormal T wave pattern in the region V-3 through V-5, best interpreted as evidence of abnormal repolarization over the area of old infarction. The intravenous administration of histamine was resumed according to my standard method. Claudication tests were carried out daily just as they had been previously. He could walk 400 to 600 steps without the development of pain. Improvement was noted after about two and a half weeks, and at the time of his dismissal he again could walk 1,600 steps without the development of intermittent claudication, but substernal pain did develop. This pain extended to the left arm and disappeared when he rested. He received 37 intravenous injections of histamine at this visit to the clinic.

Comment on Case 8—In this case, tolerance for exercise, as manifested by freedom from intermittent claudication of the left lower extremity and from thoracic pain, was definitely increased. We were extremely careful to check his walking at the same time each day and under exactly the same environmental conditions. Special care was taken to see that he walked at the same speed and that he did not slow down when turning at the end of the corridor. The result obtained in this case indicates that the intravenous administration of histamine diphosphate does increase blood flow to the extremities and most probably to the myocardium. During his stay in Rochester, the patient did not change any of his habits except to discontinue the use of tobacco. It could not be determined definitely whether he ever had had myocardial infarction or not. Before he came to the clinic, he had had substernal pain while at rest.

I have made comparable studies of a small number of other cases of chronic occlusive arterial disease and have found that the patients have responded in a similar manner.

An additional observation which may be of interest was the fact that the patient was baldheaded when he first came to the clinic. What hair he did have around his head was black in color. He received a total of 51 intravenous injections of histamine during his first visit to the clinic. After returning home, he noted a definite growth of what he termed "blonde baby hair" over the top of his head. This was noticed and commented on by many of his friends and business associates.

Case 9. Right hemiparesis and aphasia resulting from a cerebral vascular accident—A man, aged 43 years, came to the clinic January 31, 1949, and was under observation through February 9, 1949. Right hemiparesis and partial aphasia had developed 17 days be-

fore he came to the clinic. There had been a tendency for slight improvement, but his family physician had suspected the presence of tumor of the brain and, therefore, had referred the patient to the clinic. Neurologic examination revealed right hemiparesis and minimal expressive aphasia, slight asymmetry of the face, and a decrease of 50 per cent in the strength of the right hand. As the patient walked he tended to swing the right leg outward and to scrape the toe of the shoe on the floor. The Babinski reflex was positive on the right side. The blood pressure was 140 mm. systolic and 95 mm. diastolic. Examination of the ocular fundi and the visual fields did not disclose any significant abnormality. Roentgenograms of the head and thorax were normal. The urine was normal. The erythrocyte count was 4,500,000 and the leukocyte count was 8,200. The differential leukocyte count was normal. A serologic test did not disclose any evidence of syphilis. The value for the hemoglobin was 13.7 gm. per 100 cc. of blood, and examination disclosed a slight increase in the value for the plasma lipids. Electroencephalography did not disclose any significant abnormality. On the twenty-third day after onset of the hemiparesis, intravenous administration of a 1:250,000 solution of histamine was started at the rate of 24 drops per minute and the rate was increased gradually to 32 drops per minute. A slight flushing of the face was evident but headache did not occur. Injection was continued for 65 minutes. There was no appreciable change in the blood pressure, which was recorded at frequent intervals. Within 10 minutes after the injection was started, the patient noted improvement in his ability to move his lips and to express himself more clearly. Definite improvement occurred in the strength of the right hand and leg, and there was approximately 50 per cent improvement in facial movements at the end of 35 minutes. At the completion of the injection, there was a 60 per cent improvement in the strength of the right hand and right lower extremity, the face was symmetrical, and the speech free. The positive Babinski reflex had become negative. Immediately after the completion of the injection, the patient got up and walked in an almost normal manner. The patient seemed amazed that improvement could have taken place so rapidly. As he expressed it, "This is the greatest moment of my life." A neurologic consultant observed the patient while he was being treated.

Comment on Case 9—In this case, it was especially interesting to note that improvement began within 10 minutes after the injection of histamine was started and that it continued throughout the course of the treatment. This seems significant. The neurologist said, "Had I not seen the response I should not have believed it. The patient made a striking improvement during treatment." Approximately three hours later, the patient played the pipe organ for the first time since the onset of his illness 23 days previously.

"Stroke" constitutes a serious clinical problem. I feel that the use of histamine in cases of this condition may serve to rehabilitate many patients if treatment is carried out promptly and if the condition has not existed for a long time. The hemiparesis in this case was probably the result of vasospasm and not the result of cerebral hemorrhage or cerebral thrombosis.

FIGURE 4. Appearance of left corneal ulcer at the time intravenous administration of histamine was started (case 10).

HISTAMINE can be used to re-establish collateral circulation following surgical ligation of the internal carotid artery. Recently, I had occasion to observe a woman, aged 49 years, who had had the left internal carotid artery ligated intracranially because of pulsating left exophthalmos, and a right hemiplegia developed immediately thereafter.

At the time I saw her she was still under the influence of the anesthetic and did not respond to questioning. She could move the left arm and leg but not the right arm and leg. I administered histamine intravenously according to my standard method, and she made approximately a 75 per cent recovery during the hour and a half that treatment was continued. In talking with her a few hours later after the effects of the anesthetic had worn off, she was quite normal and was not aware of the fact that she had had a hemiplegia.

Case 10. Recurrent corneal ulcers—A man, aged 37 years, registered at the clinic on October 1, 1945. He was seen in the Section on Ophthalmology because he complained of redness, excessive lacrimation and a drawing sensation in the left eye. These symptoms had been present for 48 hours. Examination revealed a circular white area at about the 9 o'clock position at the limbus of the left eye. The area was stained with fluorescein. Extending from this area to very close to the margin of the cornea was a small adjacent area which did not stain with fluorescein. Local treatment was employed on seven consecutive days. On October 6 and again on October 8, the ulcer was cauterized with tincture of iodine, which did not produce definite improvement.

The results of general physical examination were essentially normal except for the presence of a left inguinal hernia which he was planning to have repaired shortly. He had been seen at the clinic on numerous occasions since 1928, chiefly because of hay fever, vasomotor rhinitis and occasional attacks of asthma.

I first saw the patient in consultation on the afternoon of October 8, 1945, at which time the corneal ulcer of the left eye was still present (Figure 4). I administered an 0.0011 per cent solution of histamine diphosphate intravenously at the rate of 28 drops per minute, and gradually increased the rate to 40 drops per minute. In the course of the first injection, the patient noted definite subjective improvement and cessation of the drawing sensation in the eye. This was especially interesting in view of the fact that there was no definite change in the appearance of the involved eye. Twenty-four hours later, the eye felt entirely normal, subjectively, and remained that way. Treatment was continued twice daily for three consecutive days, at which time he was dismissed from my care. At that time, the eye appeared normal.

He has been seen at the clinic on 13 subsequent occasions because of recurrent marginal ulcers in either the right or left eye. Histamine diphosphate was always administered intravenously, twice daily, but was not supplemented by local treatment. On the various occasions from 2 to 16 intravenous injections of histamine were required to eradicate the objective signs completely, although they have disappeared in 21 to 24 hours. Subjective improvement nearly always was noted in the course of, or shortly after, the first injection. Apparently no definite scarring of the cornea of any clinical significance has been noted following the various ulcers.

I also have had a similar experience in treating the patient's older brother who has had recurrent marginal ulcers and has been under my observation on seven occasions.

Comment on Case 10—At the time I first saw the patient in this case, I did not know whether intravenous histamine therapy would prove of any value or not. The manner in which both he and his brother have responded to this therapy on so many occasions leaves little doubt as to the value of histamine in the treatment of their corneal ulcers. I think a more extensive therapeutic trial of this drug is warranted in similar cases.

Both patients are convinced that histamine therapy produces prompt subjective relief and shortens the clinical course of the ulcers. These men are both local residents, and I have had the opportunity of observing them for a relatively long period of time.

Case 11. Histaminic cephalgia (Horton's syndrome) and early observations regarding histamine sensitivity and compound E (cortisone)—A woman, aged 38 years, first came to the clinic on April 6, 1936, because of attacks of pain in the left side of the head and face. The onset of the pain had occurred 13 years previously. The pain usually had occurred at night and had lasted about 15 minutes. It always had involved the left side of the head as well as the neck, and the involved area had corresponded in general to the distribution of the external carotid artery. The attacks had lasted several weeks or even months, and had been followed by periods of remission which had lasted for several months. Each series of attacks seemed to be somewhat more severe than the previous ones. She had had as many as 10 attacks in 24 hours.

The results of general physical examination were essentially normal. A roentgenogram of the head was normal except for the presence of sclerosis in the right mastoid area. The results of neurologic examination were normal except for the presence of slight anesthesia over the left infra-orbital area, which was the result of 7 injections of alcohol which had been given through the roof of the mouth in an attempt to block the pain fibers of the second division of the trigeminal nerve on the left side. No trigger zones were present, and the attacks had not been associated with vomiting. She referred to her attacks as "left face pain." A tentative diagnosis of atypical face pain was made but no treatment was advised.

When she returned to the clinic on May 15, 1940, more detailed history revealed that we were dealing with the new syndrome histaminic cephalgia, which had been under special investigation during the previous three years. The attacks had been practically identical with the previous attacks, but they had occurred more frequently and had been more severe. They always had involved the left side of the head, face and neck. The distribution of the pain had not corresponded to that of the left trigeminal nerve. During an attack, the left eye had watered profusely, the left nostril had become plugged, and the pain often had been severe enough to make her scream. She said that she had consulted more than 20 physicians in addition to a number of osteopaths and chiropractors, and that the various types of therapy had not relieved the pain.

The results of routine physical examination and neurologic examination were essentially normal. A diagnosis of left histaminic cephalgia was made.

The subcutaneous administration of 0.65 mg. of histamine base, as a provocative test, precipitated a typical attack. (I now use 0.35 mg. histamine base for the standard provocative test.) Her husband, who observed her, remarked, "This is a typical attack." At the height of the pain, I compressed the left common carotid artery and she immediately became unconscious and had a slight convulsion. She was lifted from a chair to a cot, and promptly regained consciousness. She did not seem to be aware of the fact that she had had a convulsion. I assumed that a sensitive carotid sinus was responsible for this phase of the clinical picture, because I had not seen it occur otherwise.

The intravenous administration of a 1:500,000 solution of epinephrine stopped the induced attack promptly. On another occasion, special examination of the ocular fundi was made by an ophthalmologist after an attack of left histaminic cephalgia had been provoked by the subcutaneous administration of 0.5 mg. of histamine base. He did not note any particular change in the appearance of the ocular fundi.

Histamine desensitization was carried out for three weeks and produced marked improvement in her symptoms, although she was having an occasional mild attack at the time of her dismissal. She did not continue to take the daily maintenance dose of histamine, and the attacks recurred the following spring.

On March 19, 1941, she returned to the clinic because attacks of histaminic cephalgia had recurred on the left side during the previous six weeks. They had

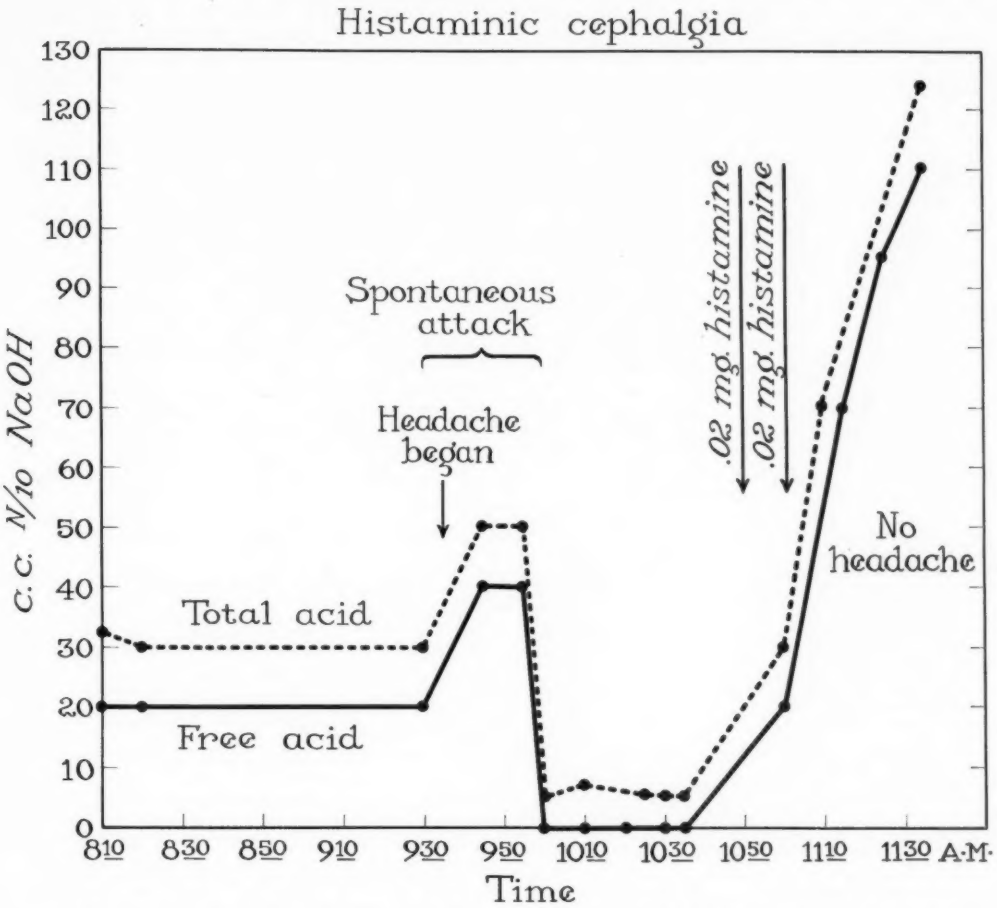


FIGURE 5. Increase in acidity of gastric contents during a spontaneous attack of left histaminic cephalgia in case 11. Approximately 40 minutes after the spontaneous attack had subsided, 0.02 mg. histamine base was administered subcutaneously, and, approximately 10 minutes later, another subcutaneous injection of 0.02 mg. histamine base was administered subcutaneously. No headache developed but there was a marked rise in gastric acidity. This indicates that the sensitized cells in the left orbital region were refractory to histamine at the time the 2 injections of histamine were administered, owing to the fact that the patient had just recovered from a spontaneous attack of left histaminic cephalgia, whereas, the gastric mucosa was still sensitive to histamine and responded in an exaggerated manner. The rise in gastric acidity depicted in the spontaneous attack was exactly the same as that provoked by the subcutaneous administration of 0.01 mg. of histamine base. This same amount of histamine had invariably provoked attacks of histaminic cephalgia on many previous occasions. Furthermore, this amount of histamine did not provoke a rise in gastric acidity in a normal subject.

been occurring every three or four hours, day and night, but had seemed worse at night. They had awakened her from sound sleep and had forced her to get out of bed. The pain had seemed to develop suddenly and had lasted for perhaps 10 to 15 minutes. Watering of the left eye and plugging of the left nostril had occurred with each attack. The distribution of the pain had been the same as it had been previously. Because of the frequency and severity of the pain, it was necessary to hospitalize the patient. Again, the results of general physical examination and neurologic examination were not significant.

The response of the acidity of the gastric contents was studied during 3 spontaneous attacks of histaminic cephalgia, and in each instance there was a rise comparable to that induced by the subcutaneous administration of 0.01 mg. of histamine base (Figure 5). This amount of histamine did not induce any increase in the acidity of the gastric contents of a normal control subject. Immediately after the cessation

of a spontaneous attack of histaminic cephalgia, I was unable to reproduce an attack of histaminic cephalgia by administering 0.04 mg. of histamine base subcutaneously, but the histamine did cause an increase in the acidity of the gastric contents that was quite dramatic. This observation indicated that the gastric mucosa was still capable of responding to minute amounts of histamine, whereas a certain length of time had to elapse before the mechanism involved in the production of the attacks of histaminic cephalgia could again be repeated.

Histamine desensitization proved most difficult at this visit. I again attempted to carry out my standard method of treatment, but observed that an attack of histaminic cephalgia on the left side was precipitated by each subcutaneous injection of histamine. After the administration of even the smallest amounts of histamine, an attack developed within 25 minutes. My notes read as follows: "On March 28, 1941, at 11:30 A.M. she was given 20 mg. of compound E (now known as cortisone) intramuscularly. No other treatment was administered that day or night. The following morning she was given 0.02 mg. of histamine base subcutaneously and she noted marked flushing of the face with a pulsating sensation in the head but no headache developed. This was the first time an injection of histamine had failed to produce an attack during this particular visit to the clinic. On March 31 she was given 40 mg. of compound E intramuscularly. I was then able to administer an 0.0011 per cent solution of histamine diphosphate intravenously without precipitating an attack." I also made the following note: "This patient was under observation at St. Marys Hospital from March 19 to April 16, 1941, but from the time of admission until March 29 even the giving of minute amounts of histamine produced one of her left histaminic cephalgia attacks. The giving of compound E on March 28 and March 31 seemed to make her less sensitive to histamine. It was only after the giving of compound E that we were able to give histamine for the first time without precipitating one of her attacks. It was then possible to carry out a routine desensitization schedule twice daily. However, the amounts have been smaller than those which we usually employ."

It is interesting to note that when she came to the clinic she was having attacks every three to four hours, day and night, and at the time of her dismissal on April 16, 1941, she had been entirely free from them since receiving compound E. She was taught to inject the histamine subcutaneously, and was advised to continue the injections daily at her home.

Comment on Case 11—This case is of unusual interest since it permitted me to demonstrate for the first time that compound E could be used to alter the patient's sensitivity to histamine. I did not fully appreciate the use of compound E at that time, although my extensive notes clearly indicated that the patient's sensitivity to histamine could be definitely altered with the use of this new hormone.

Case 12. Histaminic cephalgia (Horton's syndrome) associated with gastric and duodenal ulcers and vasomotor rhinitis—A man, aged 54 years, first registered at the clinic on March 11, 1947. Recurrent attacks of left hemicrania had begun to occur in 1936. Each attack had lasted for from 30 minutes to an hour. The pain had not been associated with nausea, vomiting or cortical phenomena, but his stomach had felt "agitated" and he had a sensation of "butterflies" in his stomach during a given attack. His epigastric symptoms which he failed to mention at the time of his routine physical examination at the clinic and which he casually referred to later as either a sensation of "butterflies" or an "agitated" stomach apparently had been accentuated with each series of attacks of left hemicrania. During an attack of pain which he described as being "excruciating" in character, the left eye had become bloodshot and had watered profusely, and both nostrils had seemed to become plugged.

The attacks almost invariably had occurred at night. The pain had awakened him from a sound sleep and had forced him to get out of bed immediately. It had seemed to originate in the maxillary region, spread into the left eye and then into the temporal region. In the more severe attacks, it had seemed to extend into the back of the head. A residual soreness had persisted in the involved area after each attack. Although the pain had not extended into the teeth, he had had practically all of his teeth extracted over a period of years on the advice of his physicians.

The nightly attacks of left hemicrania had continued to recur at frequent intervals for seven consecutive years. He then had experienced four years of freedom from the pain. He had not had gastric symptoms of any type during this period.

About three months before he came to the clinic, a series of attacks had occurred on the right side. They were identical in every respect with those he had previously had on the left side except that the right eye had seemed to become even more bloodshot than the left one had during the previous series of attacks involving the other side.

Just before he came to the clinic, he had received subcutaneous injections of histamine diphosphate daily for 10 days in the hope of preventing the attacks. The first injection had brought on an attack, and he said, "The last one almost knocked me out completely." The physician who had treated him had used a solution containing 2.75 mg. of histamine diphosphate per cubic centimeter. This is 10 times stronger than the one I employ in administering the drug subcutaneously. He had noted that his face was flushed after each injection. Headache also had developed and a sensation of "butterflies" had been present in the epigastric region. When he came to the clinic, he was having as many as 4 attacks in 24 hours.

Routine physical examination did not disclose any significant abnormality. His blood pressure was 120 mm. systolic and 80 mm. diastolic. Examination of the ocular fundi revealed healed chorioretinitis in the left eye. Examination by an otolaryngologist revealed a small polyp in the middle meatus. The nasal mucous membrane was pale and edematous, and there was a marked deviation of the nasal septum to the right.

The urine was normal. The concentration of hemoglobin was 15.5 gm. per 100 cc. of blood and the leukocyte count was 9,700. The results of dental

examination were normal. A routine serologic test did not disclose any evidence of syphilis. Roentgenographic examination of the head revealed numerous metallic fragments in the soft tissues of the left side of the face and head, as well as slight calcification of the falx. These fragments were the result of shrapnel wounds received during Word War I. Although a roentgenogram of the accessory nasal sinuses disclosed pansinusitis, there was no clinical evidence of active infection. A roentgenogram of the thorax was normal.

The attacks of pain in the right side of the head had been recurring almost nightly for three months. At the time I saw the patient, the only actual pain he had experienced was the pain in the head. There was no history to suggest the presence of a peptic ulcer, and he and his wife both insisted that he had not had any gastrointestinal distress between the attacks of pain in the head. Roentgenographic examination of the stomach and duodenum was not performed at the time of his routine general examination since there were no symptoms to indicate the necessity for such a test. The acidity of the gastric contents was determined by the method of Töpfer. The value for the total acidity ranged from 22 to 28 and that for the free hydrochloric acid ranged from 8 to 16.

The diagnosis was histaminic cephalgia and vasomotor rhinitis.

Just before histamine desensitization was started, 9 cc. of Kendall's whole cortical extract was administered intravenously because the patient had received overdoses of histamine before he came to the clinic. The administration of the whole cortical extract was repeated at frequent intervals while the patient was at the clinic. On March 20, 1947, histamine desensitization was begun by administering a 1:10,000 solution of histamine diphosphate subcutaneously. The initial dose was 0.1 cc. and the maximal dose was 0.55 cc. The drug was administered twice a day.

As previously stated, the patient was having a sensation of "butterflies" in the epigastrium when histamine desensitization was started, but he said that the symptoms were abating. After histamine desensitization had been continued for eight days, the epigastric distress continued to recur about 11:30 A.M., 3 P.M., and also in association with nocturnal attacks of pain in the head.

On March 29, roentgenographic examination of the stomach and duodenum disclosed evidence of a duodenal ulcer, but the roentgenologist could not be certain about the condition of the stomach. Two days later, similar examination revealed a small ulcer on the lesser curvature, just proximal to the pylorus, and also disclosed the duodenal ulcer. The subcutaneous injection of histamine diphosphate was continued twice daily. On April 15, roentgenographic examination did not disclose evidence of either a gastric ulcer or a duodenal ulcer.

The patient had been accustomed to eating food between meals, but he had failed to mention this fact. Although the attacks of histaminic cephalgia ceased on April 21, the subcutaneous administration of histamine diphosphate was continued twice daily until May 9, when the patient was dismissed. He had been taught to inject the drug subcutaneously, and was advised to continue to inject 0.4 cc. of the solution daily at home. There was a 75 per cent improvement in the vasomotor rhinitis, and the stuffy feeling in the nose had largely disappeared. However, the nasal polyp remained.

He returned to the clinic on September 1, 1947, and again on September 6, 1948, but said that he had not had any recurrence of the histaminic cephalgia or symptoms of peptic ulcer. The primary reason for his returning to the clinic was angina pectoris and myocardial infarction.

Comment on Case 12—In this case, the history was typical of histaminic cephalgia. It is interesting to note that although the patient had had attacks involving both the right and left sides of the head, the pain did not shift from side to side in a given series of attacks, and he did not have nausea, vomiting or cortical phenomena, which often occur in cases of migraine.

I INSTITUTED histamine desensitization because I had observed other cases of histaminic cephalgia and duodenal ulcer in which the attacks of histaminic cephalgia had ceased and the ulcers had healed promptly after the use of this type of therapy. Hence, I did not alter the histamine desensitization schedule in this case, but gave the patient subcutaneous injections of the drug twice daily, according to my standard method. The attacks of histaminic cephalgia ceased after four consecutive weeks of treatment, and the peptic ulcers healed even before that time.

Ordinarily one might think that the administration of histamine would be contraindicated in the presence of peptic ulcer, but such is not the case.

I have previously called attention to the relationship between acute duodenal ulcer and histaminic cephalgia.[55] The formation of the ulcer in each instance has been secondary to, or has occurred simultaneously with the onset of the attacks of, histaminic cephalgia. During a given attack of histaminic cephalgia, the acidity of the gastric contents frequently increases to an abnormally high level. This increase is comparable to that which is induced by the subcutaneous injection of known amounts of histamine (Figure 6). I have demonstrated that some persons are hypersensitive to histamine—so much so that even the administration of 0.01 mg. of histamine base has been sufficient to precipitate an increase in the acidity of the gastric contents. The administration of the same amount of histamine also has provoked an attack of histaminic cephalgia.

It is interesting to note that in this case the acidity of the gastric contents was normal or below normal.

Although histaminic cephalgia is a medical problem, in 40 per cent of the cases which I have observed during the past decade the patients had undergone unnecessary operations, some of which

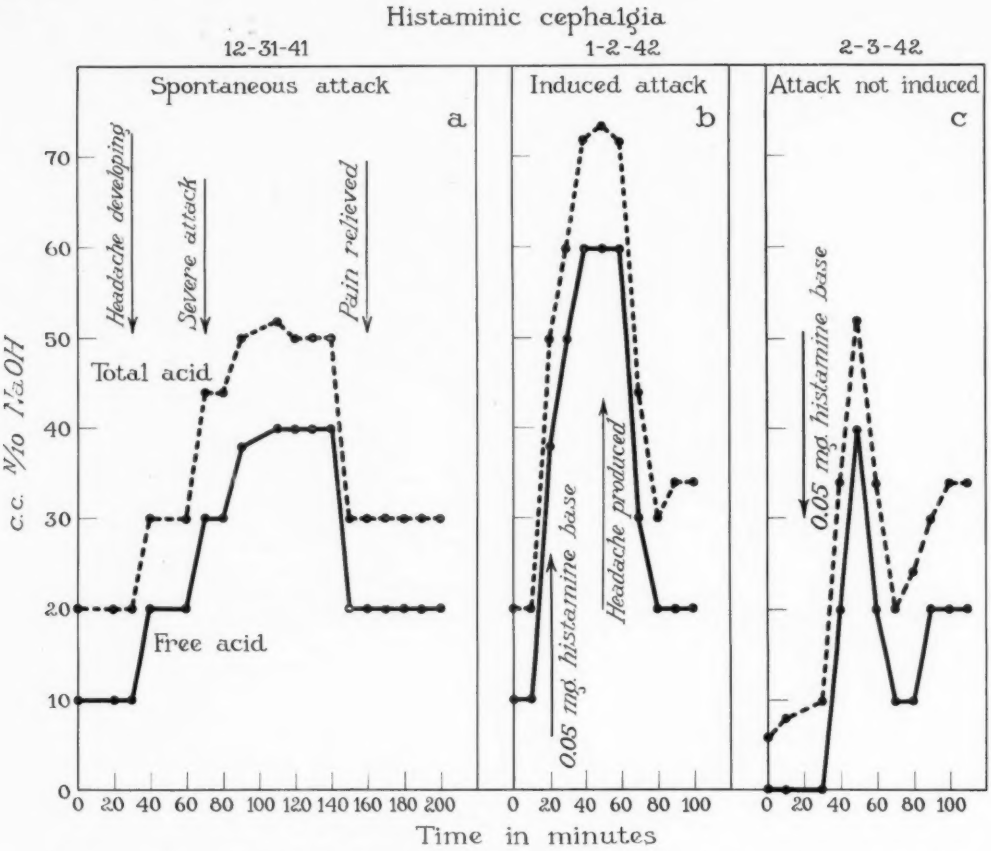


FIGURE 6*a*. Increase in gastric acidity which occurred during a spontaneous attack of histaminic cephalgia. *b*. Increase in gastric acidity observed during an induced attack of histaminic cephalgia. The attack was provoked by the subcutaneous administration of 0.05 mg. histamine base. On January 3, 1942, histamine desensitization was instituted according to my standard method. The spontaneous attacks of histaminic cephalgia ceased after approximately three weeks. *c*. Increase in gastric acidity observed after the subcutaneous administration of 0.05 mg. of histamine base. This amount of histamine did not provoke an attack of histaminic cephalgia which had occurred on January 2, 1942 (*b*). The rise in gastric acidity is less marked than that observed prior to histamine desensitization.

have been major in character, such as ligation of the middle meningeal and external carotid arteries, cervical sympathectomy, extensive intranasal operations and injection of alcohol into 1 or more branches of the trigeminal nerve. All of the teeth had been extracted in some cases. However, none of these procedures had been of any help. Of the many patients I have seen with histaminic cephalgia, all of them were incapacitated at the time of arrival at the clinic. Ninety-two per cent have obtained complete relief from their attacks by means of histamine desensitization, although most of them have experienced a recurrence of symptoms at a later date, which required further adjustment of the dosage or a repetition of the histamine desensitization schedule.

Case 13. Ménière's disease—Original observations regarding treatment of acute vertigo and deafness—A physician's wife, aged 38 years, was seen at the clinic on November 23, 1939, during an acute attack of vertigo associated with some nausea, vomiting, tinnitus and a marked loss of hearing in the left ear. She also had a sensation of fullness in the left ear. The neurologist who examined the patient made a note indicating that she could not understand normal conversation with the left ear. She had been incapacitated for about three weeks with similar recurring attacks. The only significant finding in her routine general exam-

ination was stiffness in the hands, which prevented her from making a fist. A roentgenogram revealed slight hypertrophic changes in the interphalangeal joints.

She had mild vertigo at the time treatment was started. I administered an 0.0011 per cent solution of histamine diphosphate intravenously at the rate of 104 drops per minute, but, after a few minutes, the rate was reduced to 74 drops per minute and maintained at that rate. After receiving only 1 mg. histamine base during the first treatment, she estimated that she had obtained 75 per cent improvement in the tinnitus and said that the sensation of fullness had disappeared. The neurologist stated, "Before administration of histamine was started, the patient was unable to hear with the left ear." Immediately after the treatment, he said, "She is able to hear sentences spoken in moderate tones." I administered histamine in the same manner the following day, and again three days later. She was the second patient with Ménière's disease to be treated in this manner. She was allowed to go home, and I awaited future developments. At the time of her dismissal, the neurologist summarized the result by making the following notation on the clinical record: "No vertigo noted in any posture or with any change in position. Head noise and tinnitus disappeared; hearing subjectively improved; no pain or swelling of joints; able to close fist tightly for first time in six years. Excellent result."

I AGAIN observed the patient on February 21, 1940, at which time she was having an acute attack of vertigo, tinnitus in the left ear, nausea, vomiting and a sensation of pressure in the head. She was brought to my laboratory in a wheel chair. The room appeared to whirl violently and she was unable to sit up alone or walk. I again administered histamine intravenously, and the following notation was made: "The nausea was markedly reduced in five minutes and had completely disappeared in approximately eight minutes after treatment was started; the bed stopped whirling within 15 minutes, and the tinnitus disappeared at the end of an hour." She was then able to get up and walk without assistance. She commented, "The injection simply worked wonders."

This patient's husband has continued to give her almost daily subcutaneous histamine injections during the past decade, and she is still getting along satisfactorily. When I saw her in consultation in January, 1948, her husband was very much impressed with the fact that she had remained relatively free from head colds since she had been receiving histamine therapy, whereas prior to that time she had been very susceptible to them.

Comment on Case 13—It is interesting to note that this patient observed a definite improvement of the hearing in the left ear after the first intravenous injection of histamine, and there was also a marked improvement in the tinnitus. Just as instructive is the fact that after only three treatments she was able to make a fist for the first time in six years. I failed to fully appreciate the disappearance of her arthritic symptoms and the improvement of the hearing at that time because I was primarily concerned with the relief of the vertigo. The opening sentence in my original publication with Shelden[41] was, "Our purpose in presenting this form of therapy is to make available to the medical profession a quick and ready method for controlling the acute symptoms in Ménière's disease." It did not occur to me that the deafness resulting from Ménière's disease could be successfully treated. In a paper I published in 1941,[42] entitled "The Use of Histamine in Ménière's Disease," I casually mentioned the fact that, of 49 patients treated with histamine at that time, a small number obtained improvement in hearing. In 1944, Lillie, Thornell and I[56] again demonstrated that the loss of hearing resulting from Ménière's disease was improved in some cases by the intravenous administration of histamine.

Case 14. Acute Ménière's disease with sudden and complete loss of hearing in the right ear—A woman, aged 46 years, came to the clinic on June 27, 1943, because of acute Ménière's disease and complete loss of hearing in the right ear, which had been present for 72 hours at the time I saw her in consultation with Dr. B. E. Hempstead, a consultant in the Section on Otolaryngology and Rhinology. The loss of hearing had occurred simultaneously with the onset of acute vertigo, nausea and vomiting. She also had some tinnitus in the left ear. Her blood pressure was 130 mm. systolic and 75 mm. diastolic. General physical examination did not disclose any significant findings.

Histamine diphosphate was administered intravenously according to my standard method. She obtained prompt relief of the vertigo, although the sensation of fullness in the right ear continued. A definite improvement of hearing was noted within four days. I treated her daily for a period of 18 days. In the first 7 intravenous injections, the drug was administered in an 0.8 per cent isotonic solution of potassium chloride; in the following 11 injections, it was given in a 0.9 per cent solution of sodium chloride. Dr. Hempstead said, "She could well have remained deaf if treatment had not been attempted. I think this is a triumph for histamine."

Comment on Case 14—Dr. Hempstead was greatly impressed with the fact that the patient's hearing in the right ear returned to a normal conversational level, and he tried to stimulate my interest in this phase of Ménière's disease. That Dr. Hempstead partially succeeded in doing so, is evidenced by the statement in my article on Ménière's symptom complex in December, 1944,[43] in which I said, "I believe that loss of hearing can best be prevented, and the acute attack aborted, by the intravenous administration of histamine." I further said, "If patients are treated promptly with histamine given intravenously during the initial acute attack it seems to be possible to prevent deafness in a large percentage of cases."

Deafness resulting from Ménière's disease is a

challenge to the medical profession—one which has not been fully met at the present time.

The factor most likely responsible for Ménière's disease is local alteration in the permeability of the capillary wall with secondary local edema. The pathologic picture now seems definitely established since the original observations made by Hallpike and Cairns[57] in 1938 demonstrated conclusively that Ménière's disease is due primarily to hydrops —not hemorrhage—into the labyrinth. Mygind[58] has indicated that the deafness in Ménière's disease is primarily an inner ear deafness. There appear to be 2 component parts to the problem: (1) Inner ear deafness, and (2) the injured neural elements of the organ of Corti. It would seem as if the first component is reversible and, therefore, amenable to treatment, but there remains the injured organ of Corti. This, too, in my opinion, is reversible in the early stages, but eventually degeneration of the neural elements occurs if treatment is not effective. Cases 13 and 14 substantiate this hypothesis. In the latter case, the patient had a complete loss of hearing in the right ear and yet she had a restoration of hearing to a normal conversational level. Dr. Hempstead did not feel she would have made a spontaneous recovery.

Case 15. Locomotor ataxia associated with lightning pains and morphinism—A man, aged 62 years, came to the clinic on August 16, 1944, primarily because of "crucifying attacks of lancinating pain," which had become increasingly frequent and severe over a period of 32 years. A diagnosis of locomotor ataxia had been made in 1912. Since that time, he had undergone intensive antisyphilitic therapy at frequent intervals.

TWENTY-THREE years before he came to the clinic, he had partially given up his business because the pain had incapacitated him, and, 15 months before he registered at the clinic, he had been forced to give it up entirely. When he first had begun the use of morphine 30 years before coming to the clinic he had taken ½ gr. (0.032 gm.) daily but for eight months before admission he had been taking 1½ gr. (0.1 gm.) daily, and the maximal amount taken daily had been 2¼ gr. (0.146 gm.). In addition, he had been taking 2 oz. of whiskey daily, and large quantities of acetylsalicylic acid. For nearly a year, he had spent most of his time in bed.

The attacks of pain had been occurring about every three weeks, and each one had lasted for about two days. Before he had started the use of morphine, the pain had been so severe that it had precipitated a complete shocklike state.

He was a miserable appearing man, sitting in a wheel chair with a cane clutched in his hand, when I first saw him in consultation with a neurologist. The clinical picture presented was that of advanced locomotor ataxia with the characteristic findings observed in cases of this disease entity. He could walk only with great difficulty. The blood pressure was 134 mm. systolic and 84 mm. diastolic. Urinalysis did not reveal any abnormality. The erythrocyte and leukocyte counts and the sedimentation rates of the erythrocytes were normal. The results of the Kline, Kahn, Hinton and Kolmer tests on the serum were normal. The values for the blood urea and serum bilirubin were within normal limits, and a dye test did not disclose any evidence of hepatic dysfunction. Roentgenographic examination disclosed calcification of the aorta and pelvic vessels, hypertrophic changes in the lower part of the thoracic segment and in the lumbar segment of the vertebral column, and calcification of the nucleus pulposus of the disk situated between the twelfth thoracic and first lumbar vertebrae. Proctoscopic examination disclosed 6 polyps in the rectosigmoid. These polyps were fulgurated.

When I saw the patient at the clinic, I never had treated the pain of locomotor ataxia with histamine, but this seemed an opportune time to do so. On August 26, 1944, I began the intravenous administration of an 0.0011 per cent solution of histamine diphosphate daily at the rate of 20 to 48 drops per minute. After the sixth injection had been given, I made the following notation: "I do not know whether he is better or not from the standpoint of pain. He is still taking the same amount of morphine. However, his wife says he walked six blocks yesterday, and he had not done so in two years. He seems to eat better and feels better." A neurologic consultant saw the patient from day to day and made notes regarding his progress. After the eighth injection the neurologist wrote, "Since the administration of histamine was started, he had one attack of pain, which occurred this morning and was not at all comparable to attacks he calls 'severe.' He looks better, has more endurance (walks instead of using a wheel chair), and on Saturday had only 1 gr. of morphine, which was the least amount taken in six months." After the thirteenth injection, I made the following notation: "Has been 100 per cent free from pain this week. He has continued to take the same amount of morphine." Two days later, the neurologist wrote, "Still no pain since I last saw him a week ago." He also commented on the fact that the patient had driven his car without precipitating pain. Driving invariably had precipitated pain on previous occasions. After the nineteenth injection the neurologist wrote, "He can now stand up to shave. He has been unusually active, and has gained 6 or 7 pounds since he came to the clinic. Has had no lightning pains for three weeks, except one in hand two weeks ago."

Before the patient was dismissed, he received a total of 47 intravenous histamine injections. Forty-one days after histamine therapy was started (that is, after the thirty-fourth injection), the use of morphine was discontinued entirely. He was taught to inject the histamine subcutaneously and was advised to take 0.5 cc. of histamine diphosphate daily. He was dismissed on December 1, 1944. I was away at that time, but on December 2, 1944, he wrote me the following letter:

"I am grateful to you for the histamine treatments, which, I am convinced, have permanently ended the crucifying attacks of lancinating pains.

"As you know, for years these pains could only be relieved by injections of morphine, and for the past two or three years, the attacks had been growing ever more frequent, necessitating constantly increasing doses of the drug. While I fully realized that the end could

not be far distant, it was, nevertheless, impossible to discontinue the morphine, unless some means could be provided to control the pain.

"Histamine has undoubtedly succeeded in my case. I am most thankful to say that I have had no morphine since October 6, (1944), due to cessation of pain. My weight has increased 22 pounds. My sense of well-being is unbelievably improved.

"I shall be ever grateful to you . . . for attempting the experiment."

When the patient returned for a check-up in June, 1945, he was still entirely free from lightning pains. He had gained 35 pounds (15.9 kg.). He returned in October, 1946, and again in September, 1947. He had not had any more lightning pains and had not used any morphine since October 6, 1944. He had continued to inject histamine diphosphate daily at home.

Comment on Case 15—This case represents one of the most interesting pain problems I have encountered. The manner in which histamine acts to relieve pain is not clear to me, even at the present time. It is interesting to note that the patient had had agonizing pain for 32 consecutive years, but, after the initial course of intravenous histamine therapy in 1944, no further intravenous injections were required, and the subcutaneous injections of histamine, which he continued at home, apparently proved to be an adequate substitute. The use of morphine never had to be resumed.

When I last saw the patient, elsewhere, about three years after his dismissal, I did not recognize him, but he promptly recognized me and greeted me with the unusual statement, "You saved my life." I then recalled the haggard and pathetic appearance of the man in the wheel chair, and I thought of the marked change which had occurred in the appearance of the man facing me. I then recalled his letter of December 2, 1944, and read it again when I returned to the clinic. "The histamine treatments . . . I am convinced, have permanently ended the crucifying attacks of lancinating pains. . . . Histamine has undoubtedly succeeded in my case."

GENERAL COMMENT

From the many observations which I have made over the past two decades and from those recorded in this paper, I believe the value of histamine as a therapeutic agent has been established.[14] The statement "histamine is a drug of considerable academic interest but little therapeutic importance" needs to be revised. In order to rationalize the therapeutic use of histamine in such a wide variety of clinical entities, it is necessary to appreciate fully the known pharmacologic and physiologic effects of this agent in human beings. No other drug, as far as I know, has such a wide variety of actions as those possessed by histamine. There is hardly a tissue or an organ in the human body which will not respond in some way to this powerful agent. The response to histamine is often dramatic. Its participation in normal and disturbed physiologic processes is of far greater significance than many physicians realize. I have given 90,080 intravenous injections of histamine and a comparable number of subcutaneous injections without observing any ill effects from the use of the drug. It is not necessary to hospitalize patients for such treatment.

Histamine, however, is not a cure-all in any sense of the word, but it is a useful drug if employed wisely. The similarity between the observations which I have made in the clinical use of histamine and those reported with the use of ACTH and cortisone are strikingly similar in many respects. Many of the clinical results which I have observed can best be explained by the action of histamine on the cortex of the suprarenal gland. I am convinced that histamine causes the release of cortisone. The effect of histamine is probably comparable to that of moxa which has been used for centuries.[59] It is my impression that when the complete story of histamine finally has been written it will constitute one of the most romantic chapters in the history of medicine.

REFERENCES

1. Windaus, A., and Vogt, W.: Synthesis of iminazolylethylamine. Ber. d. deutsch. chem. Gesellsch. 40:3691-3695, 1907.
2. Barger, G., and Dale, H. H.: The presence in ergot and physiological activity of β-imidazolylethylamine. J. Physiol. 40:xxxviii-xl, 1910.
3. Best, C. H., Dale, H. H., Dudley, H. W., and Thorpe, W. V.: The nature of the vaso-dilator constituents of certain tissue extracts. J. Physiol. 62:397-410, 1927.
4. Dale, H. H., and Laidlaw, P. P.: The physiological action of β-iminazolylethylamine. J. Physiol. 41:318-344, 1910.
5. von Pirquet, C.: Allergie. München. med. Wchnschr. 53:1457-1458, 1906.
6. Selle, W. A.: Histamine—its physiological, pharmacological and clinical significance. Texas Rep. Biol. & Med. 4:138-244, 1946.
7. Kwiatkowski, H.: Histamine in nervous tissue. J. Physiol. 102:32-41, 1943.
8. Code, C. F., and Macdonald, A. D.: The histamine-like activity of blood. Lancet 2:730-733, 1937.
9. Rose, Bram: Studies on blood histamine in cases of allergy. I. Blood histamine during wheal formation. J. Allergy 12:327-334, 1941.
10. Randolph, T. G., and Rackemann, F. M.: The blood histamine level in asthma and in eosinophilia. J. Allergy 12:450-456, 1941.
11. Code, C. F.: The quantitative estimation of histamine in the blood. J. Physiol. 89:257-268, 1937.
12. Barsoum, G. S., and Gaddum, J. H.: The pharmacological estimation of adenosine and histamine in blood. J. Physiol. 85:1-14, 1935.
13. Ferraro, A.: Pathology of demyelinating diseases as an allergic reaction of the brain. Arch. Neurol. & Psychiat. 52:443-483, 1944.
14. Dragstedt, C. A.: The physiological significance of histamine. Quart. Bull., Northwestern Univ. M. School 14:283, 1940.
15. Code, C. F.: A discussion of benadryl as an antihistamine substance. Proc. Staff Meet., Mayo Clin. 20:439-445, 1945.
16. Weiss, Soma, Ellis, L. B., and Robb, G. P.: Bodily responses in man during the continuous intravenous administration of histamine. (Abstr.) Am. J. Physiol. 90:551-552, 1929.
17. Goodman, Louis, and Gilman, Alfred: The Pharmacological Basis of Therapeutics, a Textbook of Pharmacology, Toxicology for Physicians and Medical Students. New York, The Macmillan Company, 1941, 1387 pp.
18. Wakim, K. G., Peters, G. A., Terrier, J. C., and Horton, B. T.: The effects of intravenously administered histamine on the peripheral circulation in man. J. Lab. & Clin. Med. 34:380-386, 1949.
19. Dille, R. S., and Horton, B. T.: Effects of various agents on pulsations of the human brain. Proc. Central Soc. Clin. Research 19:58-59, 1946.

20. Anrep, G. V.: Lane Medical Lectures: Studies on Cardiovascular Regulation. Stanford University, Calif., Stanford University Press. 1936, vol. 3, pp. 93; 111-112.
21. Essex, H. E., Wegria, R. G. E., Herrick, J. F., and Mann, F. C.: The effect of certain drugs on the coronary blood flow of the trained dog. Am. Heart J. 19:554-556, 1940.
22. Horton, B. T., Brown, G. E., and Roth, Grace M.: Hypersensitiveness to cold with local and systemic manifestations of a histamine-like character: Its amenability to treatment. J.A.M.A. 107:1263-1268, 1936.
23. Stead, E. A., Jr., and Warren, J. V.: The effect of the injection of histamine into the brachial artery on the permeability of capillaries of the forearm and hand. J. Clin. Investigation 23:279-281, 1944.
24. Peters, G. A., Horton, B. T., and Boothby, W. M.: The effect of continuous intravenous administration of histamine on basal metabolism in human beings. J. Clin. Investigation 24:611-615, 1945.
25. Popielski, L.: β-imidazolyläthylamin und die Organextrakte. I. β-imidazolyläthylamin als mächtiger Erreger der Magendrüsen. Arch. f. d. ges. Physiol. 178:214-236, 1920.
26. Carnot, P., Koskowski, W., and Libert, E.: L'influence de l'histamine sur la sécrétion des sucs digestifs chez l'homme. Compt. rend. Soc. de biol. 86:575-578, 1922.
27. Mogena, H. G.: The effect of histamine on the secretion of gastric juice. An. acad. med.-quirurg. españ. 14:683-707, 1927; (Abstr.) Chem. Abstr. 23:3025, 1929.
28. Best, C. H., and McHenry, E. W.: Histamine. Physiol. Rev. 11:371-477, 1931.
29. Peters, G. A., and Horton, B. T.: The effect of intravenous administration of histamine on gastric acids in man. Proc. Staff Meet., Mayo Clin. 15:545-549, 1940.
30. Wolf, Stewart, and Wolff, H. G.: Correlation of vascular changes with changes in motor activity and secretion in the stomach of man. Am. J. Physiol. 138:309-317, 1943.
31. Peters, G. A., and Horton, B. T.: Continuous intravenous administration of histamine: effect on the electrocardiogram and serum potassium. Am. Heart J. 27:845-857, 1944.
32. Rose, Bram, and Browne, J. S. L.: The effect of adrenalectomy on the histamine content of the tissues of the rat. Am. J. Physiol. 131:589-594, 1941.
33. Marshall, P. B.: The influence of adrenal cortical deficiency on the histamine content of rat tissues. J. Physiol. 102:180-190, 1943.
34. Gotzl, F. R., and Dragstedt, C. A.: Effect of thyroidectomy and of experimental hyperthyroidism upon histamine content of rat tissues. Proc. Soc. Exper. Biol. & Med. 45:688-691, 1940.
35. Roth, Grace M., and Kvale, W. F.: A tentative test for the diagnosis of pheochromocytoma. J. Lab. & Clin. Med. 30:366-368, 1945.
36. Kvale, W. F., Roth, Grace M., and Clagett, O. T.: Headache and paroxysmal hypertension; observations before and after the surgical removal of a pheochromocytoma. S. Clin. North America 24:922-933, 1944.
37. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G.: A test for adrenal cortical insufficiency: the response to pituitary adrenocorticotropic hormone. J.A.M.A. 137:1005-1009, 1948.
38. Last, I. H., Jordan, Paul, Pitesky, Isadore, and Bond, Epperson: The eosinophil response: Immediate vs. delayed eosinopenia. Science 112:47-49, 1950.
39. Kiely, J. P., Bain, R. C., Mathieson, D. R., and Horton, B. T.: The eosinophile response to histamine in man. Unpublished data.
40. Horton, B. T., Wagener, H. P., Aita, J. A., and Woltman, H. W.: Treatment of multiple sclerosis by the intravenous administration of histamine. (Abstr.) J.A.M.A. 124:800-801, 1944.
41. Shelden, C. H., and Horton, B. T.: Treatment of Ménière's disease with histamine administered intravenously. Proc. Staff Meet., Mayo Clin. 15:17-21, 1940.
42. Horton, B. T.: The use of histamine in Ménière's disease. Surg., Gynec. & Obst. 72:417-420, 1941.
43. Horton, B. T.: A symposium on Ménière's symptom complex: Medical point of view. Arch. Otolaryng. 40:330-332, 1944.
44. Horton, B. T., Hallberg, O. E., and Williams, H. L.: Nerve deafness; treatment by intravenous administration of histamine. Collect. Papers Mayo Clin. & Mayo Found. 38:422-423, 1946; (Abstr.) Proc. Central Soc. Clin. Research 19:79-80, 1946.
45. Hallberg, O. E., and Horton, B. T.: Sudden nerve deafness: Treatment by the intravenous administration of histamine. Proc. Staff Meet., Mayo Clin. 22:145-149, 1947.
46. Horton, B. T.: Experiences with histamine in the treatment of nerve deafness. (Abstr.) Ann. Otol., Rhin. & Laryng. 58:920-925, 1949.
47. Horton, B. T., MacLean, A. R., and Craig, W. McK.: A new syndrome of vascular headache; results of treatment with histamine and histaminase. (Abstr.) Proc. Central Soc. Clin. Research 12:30-31, 1939.
48. Horton, B. T.: The use of histamine in the treatment of specific types of headaches. J.A.M.A. 116:377-383, 1941.
49. Horton, B. T.: Symposium: Head and face pain medicine. Tr. Am. Acad. Ophth. 1944, pp. 23-33.
50. Macy, Dorothy, Jr., and Horton, B. T.: Treatment of migraine with histamine. J.A.M.A. 137:1110-1114, 1948.
51. Horton, B. T., and Macy, Dorothy, Jr.: Treatment of headache. M. Clin. North America 30:811-831, 1946.
52. Horton, B. T.: Headache: Clinical varieties and therapeutic suggestions. M. Clin. North America 33:973-1005, 1949.
53. Horton, B. T., and Wagener, H. P.: Retrobulbar neuritis: Treatment with histamine. (Abstr.) Proc. Central Soc. Clin. Research 21:58-59, 1948.
54. Iams, A. M., and Horton, B. T.: An ulcer which appeared in the stomach of a man receiving histamine intravenously. Gastroenterology 6:449-451, 1946.
55. Horton, B. T.: Histaminic cephalgia resulting in production of acute duodenal ulcer. J.A.M.A. 122:59, 1943; (Abstr.) Proc. Central Soc. Clin. Research 15:29, 1942.
56. Lillie, H. I., Horton, B. T., and Thornell, W. C.: Ménière's symptom complex: Observations on the hearing of patients treated with histamine. Ann. Otol., Rhin. & Laryng. 53:717-741, 1944.
57. Hallpike, C. S., and Cairns, H.: Observations on the pathology of Ménière's syndrome. Proc. Roy. Soc. Med. 31(pt. 2):1317-1336, 1938; J. Laryng. & Otol. 53:625-655, 1938.
58. Mygind, S. H.: Experimental-histological studies on the labyrinth. XI. Correlation of our histological and clinical experiments and observations. Conclusive review. Acta oto-laryng. 35:108-129, 1947.
59. Larrey, D. J.: On the use of the Moxa, as a therapeutic agent. (Translated by Robley Dunglison.) London, Thomas and George Underwood, 1822, 148 pp.